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ORIGINAL ARTICLES

A. M. A.
Archives of Neurology and Psychiatry

VOLUME 78 NOVEMBER 1957 NUMBER 5

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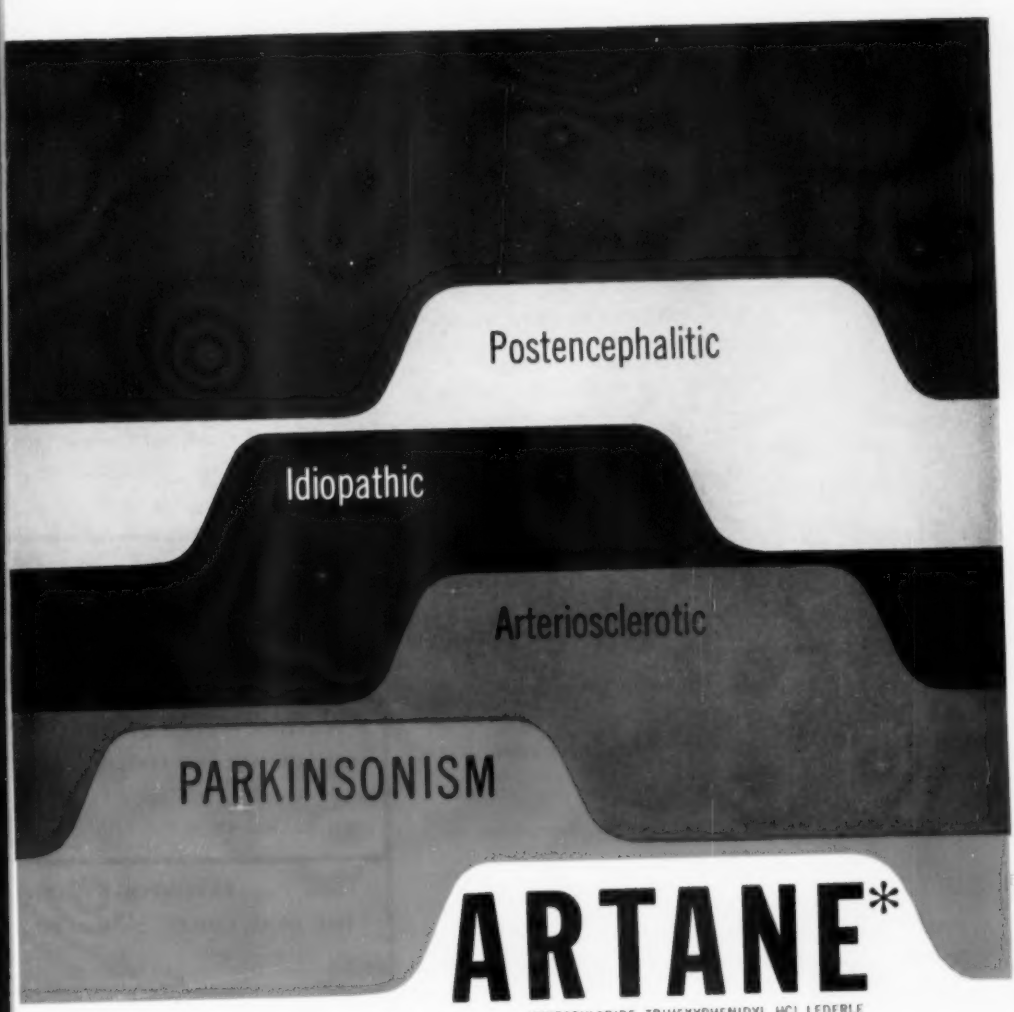

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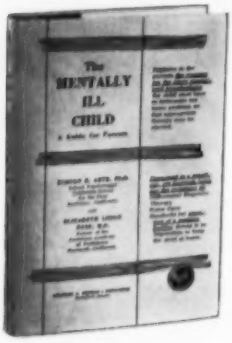

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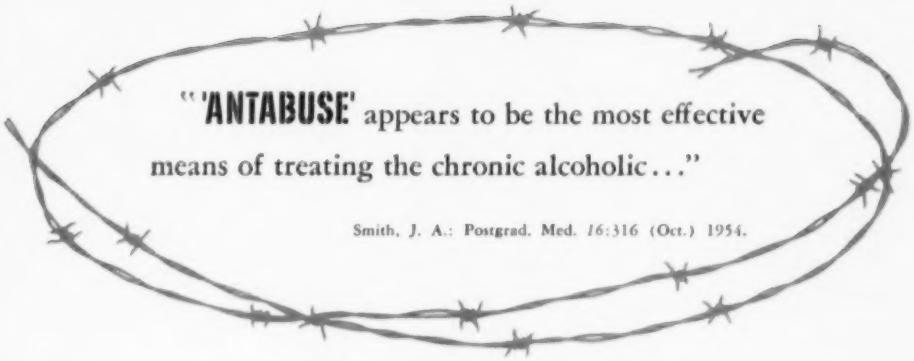

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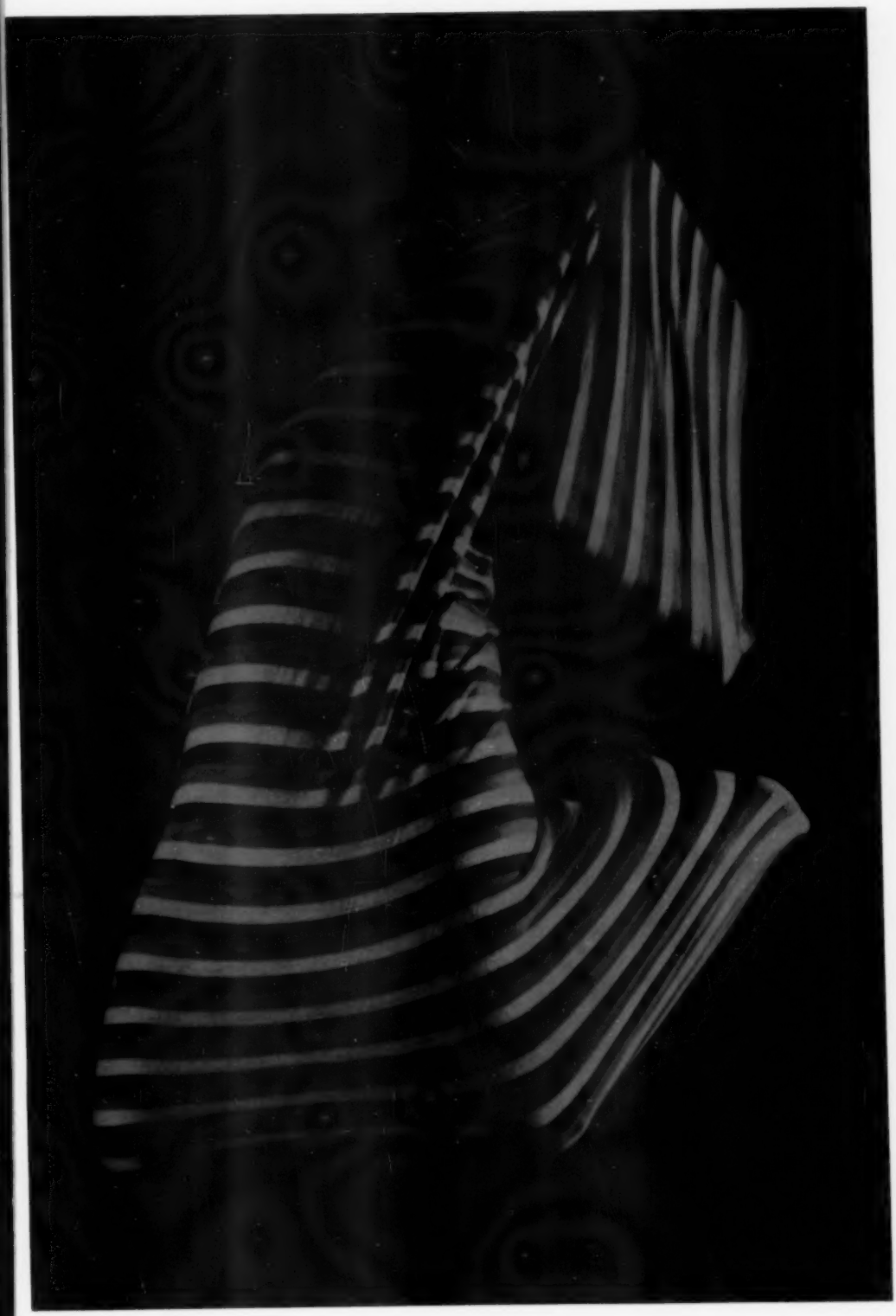

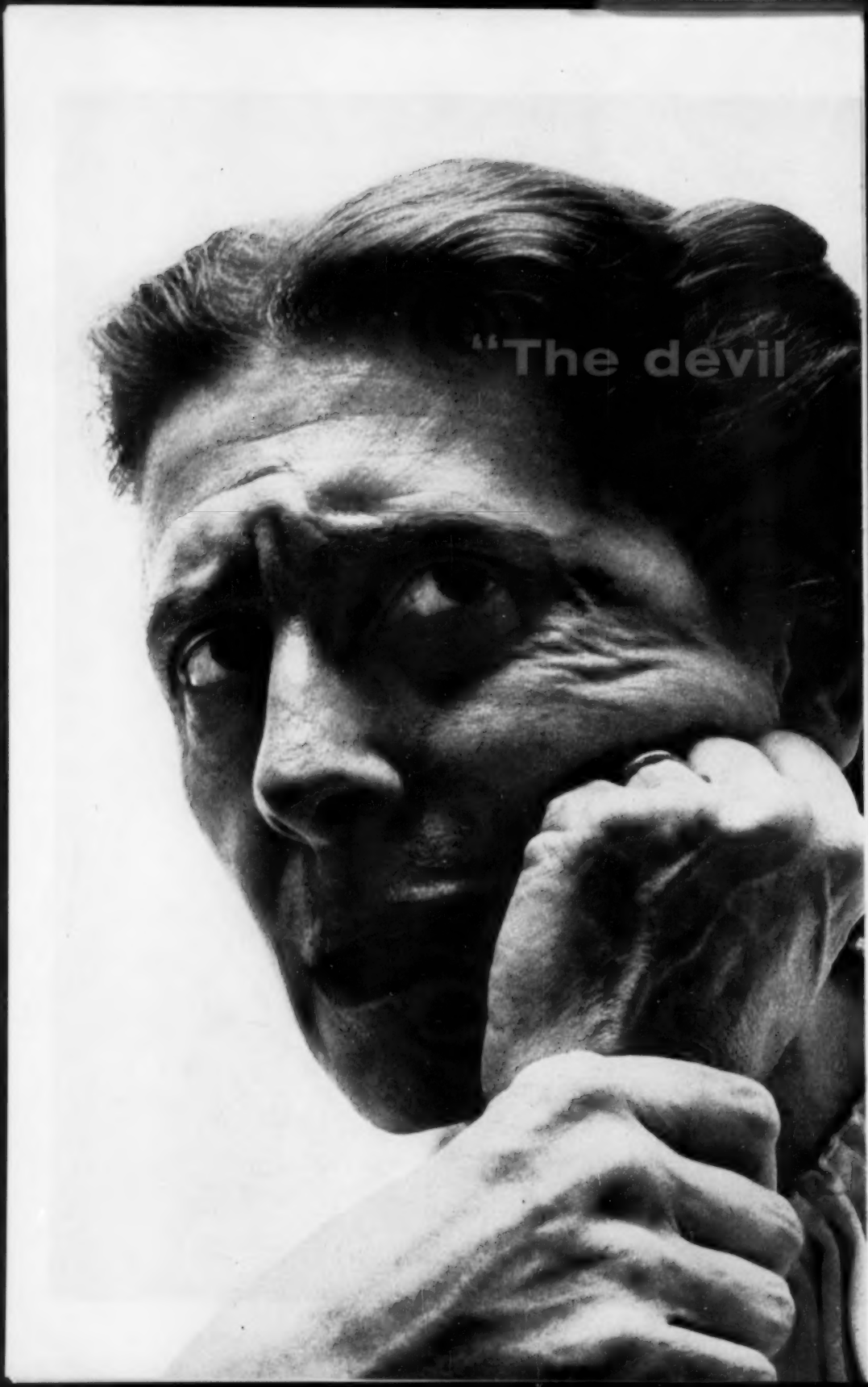
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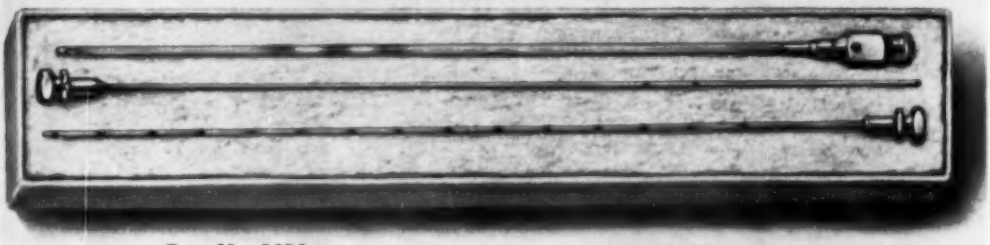

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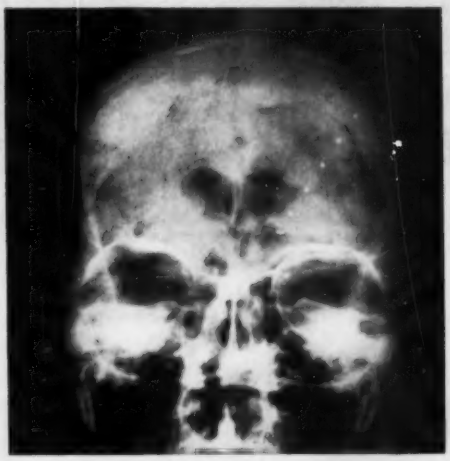

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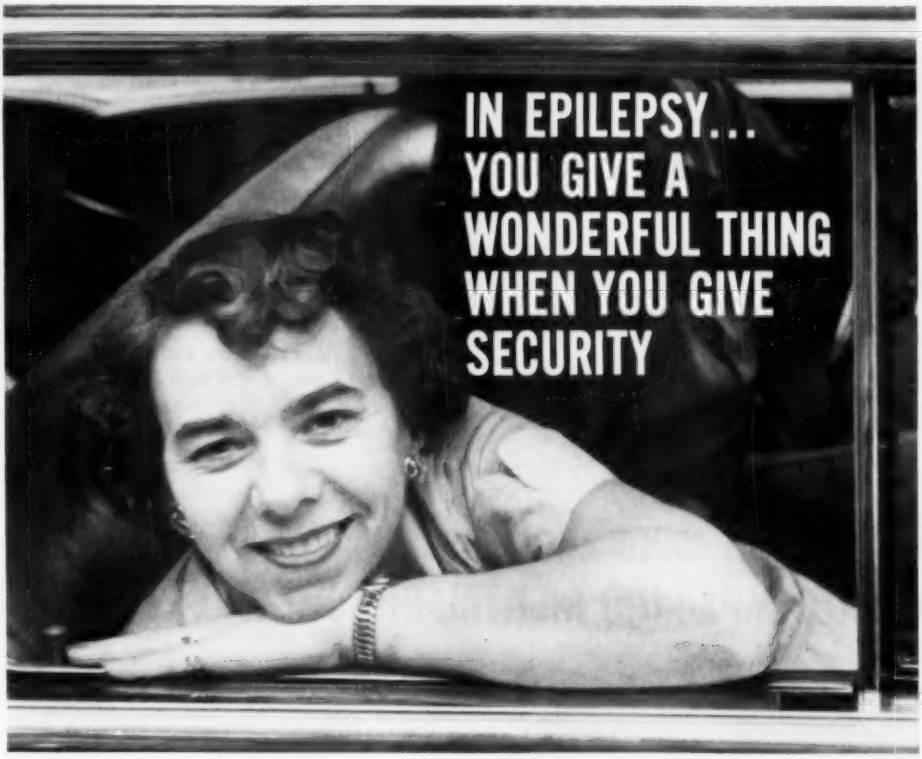
*Cooper, I. S.: Chemopallidectomy: An Investigation Technique in Geriatric Parkinsonians, Science 121: 217-218 Feb. 1955.

*Cooper, I. S.: The Neurosurgical Alleviation of Parkinsonism. Springfield, Ill.: Charles C. Thomas, Publisher. 1956.



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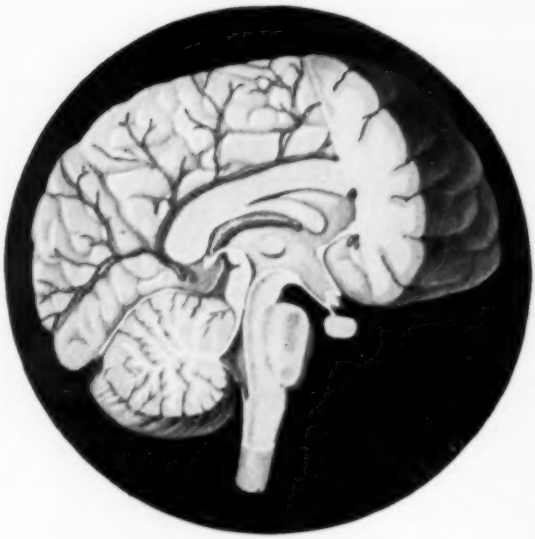

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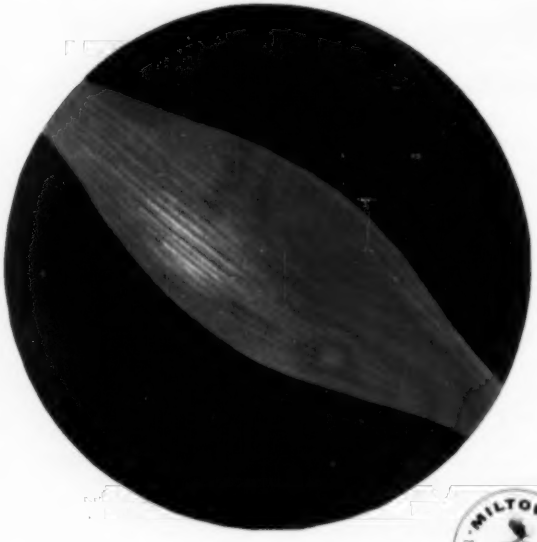

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Terminal Distribution of Spinoreticular Fibers in the Cat

GIAN FRANCO ROSSI, M.D., Pisa, Italy, and ALF BRODAL, M.D., Oslo, Norway

Fibers ascending in the spinal cord and terminating in the reticular formation of the brain stem were demonstrated around the turn of the century in experimental animals,[22,23,30,31,40] as well as in man.[15,37] After the discovery of the ascending reticular activating system by Moruzzi and Magoun,[29] renewed attention was directed to the pathways mediating spinal impulses to the reticular formation, and recent experimental anatomical investigations[6,20,21,26-28] have confirmed and extended the findings made in studies with the Marchi method by the classical workers.

In a previous study[12] we have shown that long ascending fibers, passing beyond the mesencephalon, take origin particularly from certain regions of the brain stem reticular formation. From a functional point of view it would be of interest to know whether these regions receive the majority of the spinoreticular fibers. The studies of the spinoreticular fibers found in the literature indicate that this may be so, but since the Marchi method used by most authors does not permit an exact determination of the site of termination of degenerating fibers, decisive conclusions cannot be made. This is possible only when silver impregnation methods are used, since by these methods the finest degenerating fibers, and sometimes even degenerating terminal boutons, can be identified. So far, this approach appears to have been used in two studies only, one by Johnson,[21] in the cat, and another by Mehler, Feferman, and Nauta,[26] in the monkey. Their results (published in abstract form) will be considered below.

In the present paper the results of an experimental study of the spinoreticular fibers in the cat with the Glees method[19] will be presented. We shall limit ourselves, however, to those regions of the reticular formation of the medulla, pons, and mesencephalon which do not project onto the cerebellum. The following three reticular nuclei will, therefore, not be considered: (1) the lateral reticular nucleus, or the nucleus of the lateral funiculus, whose spinal afferents * were investigated in a previous study[8]; (2) the paramedian reticular nucleus of the medulla oblongata, which has been reported on in a separate paper,[10] and (3) the nucleus reticularis tegmenti pontis, of Bechterew, to which spinal afferents have been traced previously.[39]

Accepted for publication Oct. 17, 1956.

From the Anatomical Institute, University of Oslo.

This work was done while Dr. Rossi was staying in the Anatomical Institute, University of Oslo, with a Norwegian Government Grant.

* In a previous study[8] one of us (A. B.) dealt with the spinal afferents to the lateral reticular nucleus. Although nothing was said to that effect, it has been assumed by some readers that spinal afferents to other regions of the reticular formation were not found. However, such fibers were observed also at that time, but not mentioned, since the subject of the study was restricted.

Historical Survey

When discussing fiber connections from the cord to the reticular formation, a distinction should be made, as far as is possible, between direct spinoreticular fibers, ending exclusively or at least primarily in the reticular formation, and fiber systems establishing connections with this region by way of collaterals in their course to higher levels of the brain. The latter group comprises systems such as the spinothalamic, spinotectal, and spinocerebellar tracts.

Since both groups of fibers appear to ascend in the ventrolateral funiculus, it is only when the fibers reach the medulla that it is possible to distinguish between them. In the caudal medulla fibers take off from the superficially situated spinothalamic tract, bend dorsomedially, and enter the medullary reticular formation. According to Cajal [14] and Scheibel,[34] these fibers are collaterals of ascending fibers, and the findings made in experimental Marchi studies have been interpreted in a similar way.[20,28] A fair number of these fibers pass through the lateral reticular nucleus. Other authors consider the fibers to the reticular formation to be chiefly collaterals from the ventral spinocerebellar tract.[6,7,15] In human material [15,37] collaterals to the medullary reticular formation have been found to take off from the dorsal spinocerebellar tract as well, and according to Blakeslee, Freiman, and Barrera,[7] some such fibers occur also in the monkey. Direct reticulospinal fibers were traced by Probst [30] in the dog; by Morin, Schwartz, and O'Leary [28] in Marchi material in the cat and monkey, and in studies with the Nauta silver method by Johnson [21] and by Mehler, Feferman, and Nauta [26] in the cat and monkey, respectively. Van Beusekom [6] studied them in the cat with the Häggqvist method. These fibers can be distinguished by their medial course from the spinothalamic tract. They ascend dorsomedial to the lateral reticular nucleus.

Concerning the origin of the reticulospinal fibers, information is still incomplete. Morin, Schwartz, and O'Leary [28] studied the retrograde cellular changes occurring in the spinal cord of the monkey following ventrolateral chordotomy. These authors found changes in cells of the contralateral dorsal gray matter and, to a small extent, in the ipsilateral dorsal gray matter and in cells of the contralateral ventral gray matter, as well as in the column of Clarke, the site of origin of the dorsal spinocerebellar tract. Since a chordotomy will interrupt not only direct spinoreticular fibers but also the ventrolaterally ascending tracts, which give off collaterals to the reticular formation, studies like these do not answer the question to what extent the changes observed are due to transection of direct spinoreticular fibers. For the same reason, they do not permit conclusions concerning their level of origin, although they indicate that fibers ascending in the ventrolateral funiculus come even from low levels of the cord, since cellular changes in the dorsal gray matter were found at all levels of the cord following cervical chordotomies. That fibers which terminate in, or give off collaterals to, the reticular formation may come from low levels of the cord is learned, however, from the observations by Thiele and Horsley [37] of degenerations following lesions of the lumbar cord in man and from experimental studies with chordotomies at thoracic [6,26,28] and lumbar levels.[8]

The termination of spinoreticular fibers has been described by several students, but a clear distinction cannot be made between the termination of direct fibers and those of the other group. However, there are some descriptions indicating not only that fibers ascending among those of the spinothalamic tract terminate in the lateral reticular nucleus (see Brodal [9] for details) but that some of them pass through this nucleus to the reticular formation medial and rostral to it.[20,28]

Another region in which degenerating fibers are found following lesions of the spinal cord is the medial reticular formation dorsal and rostral to the inferior olive.[6,15,20,27,28,37] To what extent collaterals from the spinothalamic tract take part in this termination is not quite clear, but from the silver

impregnation studies of Johnson [21] and of Mehler, Feferman, and Nauta [26] it appears that this is the main terminal area of the direct, medially coursing, spinoreticular fibers.

The pontine reticular formation also receives fibers from the spinal cord. Their terminal region, according to Probst,[30] is the dorsomedial reticular formation at the level of the facial nerve and the motor trigeminal nucleus, and according to Morin et al.[28] and van Beusekom,[6] the lateroventral reticular formation at the level of the superior olive, while Johnson [21] and Mehler et al.,[26] using the Nauta method, traced the fibers to a more extensive region, as will be commented upon below. Spinoreticular fibers to the midbrain reticular formation do not appear to have been described, but Johnson [21] and Mehler et al.[26] traced some fibers to the periaqueductal gray matter.

Material and Methods

Altogether, 12 adult cats have been used as experimental animals in this sudy. Some of them have been used in previous investigations of the termination of spinal afferents to the inferior olivary nucleus,[18] the lateral reticular nucleus,[8] the lateral cervical nucleus,[11] and the pontine nuclei.[29] As controls have been used the brains of some normal cats, treated in the same way as the experimental material.

The surgical procedures were performed under pentobarbital (Nembutal) anesthesia and with sterile precautions. After a laminectomy a lesion was made in the spinal cord by means of a sharp knife or a pair of scissors. The animals were killed after three to six days by exsanguination under an overdose of pentobarbital. The brain and the spinal cord were then immediately dissected free, and the brain stem, usually including the first two cervical segments, immersed in 10% formalin for fixation. After fixation the brain stem was cut on the freezing microtome in 15μ sections. In most cases the sections were made in the horizontal plane. The sections were collected in groups of 15, and of each group 2 or more sections were stained with the silver impregnation method of Glees.[10] In some cases sections were also stained with thionine to facilitate identification of nuclear groups in the silver-stained series.

The part of the cord containing the lesion was fixed in 96% alcohol, embedded in paraffin, and cut serially in transverse sections, for the identification of the lesion.

The regions of termination of spinoreticular fibers have been correlated with the cytoarchitectonic subdivisions of the reticular formation distinguished by Meessen and Olszewski,[25] as will be discussed below.

Results

Terminal Degeneration in Reticular Formation

After appropriately placed lesions of the spinal cord, degenerating terminal fibers, as well as coarser, preterminal degenerating fibers, are found in certain regions of the reticular formation (see below). The terminal degenerating fibers appear as rows of strongly argentaffine, small dots, round or ovoid (Figs. 1 and 3). Larger, dark particles of a round or more irregular shape may also be seen. When a terminal degenerating fiber is seen to be connected with such a structure, it may be interpreted as representing a degenerating terminal bouton. However, this is only occasionally observed. On account of the wide variations in the appearance of terminal boutons in Glees sections from the reticular formation of the normal cat (see Rossi and Brodal [33] for particulars), it is usually impossible to decide whether a particular bouton is normal or degenerating. When recording the degenerative changes, we have, therefore, taken into account the fibers only. The presence in a region of degenerating fine terminal fibers is taken to indicate the terminal area of transected fibers. Somewhat coarser fibers, most of which are presumably preterminal, are usually also found in the areas of termination. In addition, degenerating medium-sized and coarse fibers can be found in fiber bundles leading to the terminal areas, and indicate the course followed by the afferent parent fibers. Terminal degenerating fibers can be seen attached to the perikaryon, as well as to the cell processes of giant cells and large cells. It is difficult to decide whether the same holds true with regard to the smaller reticular neurons.

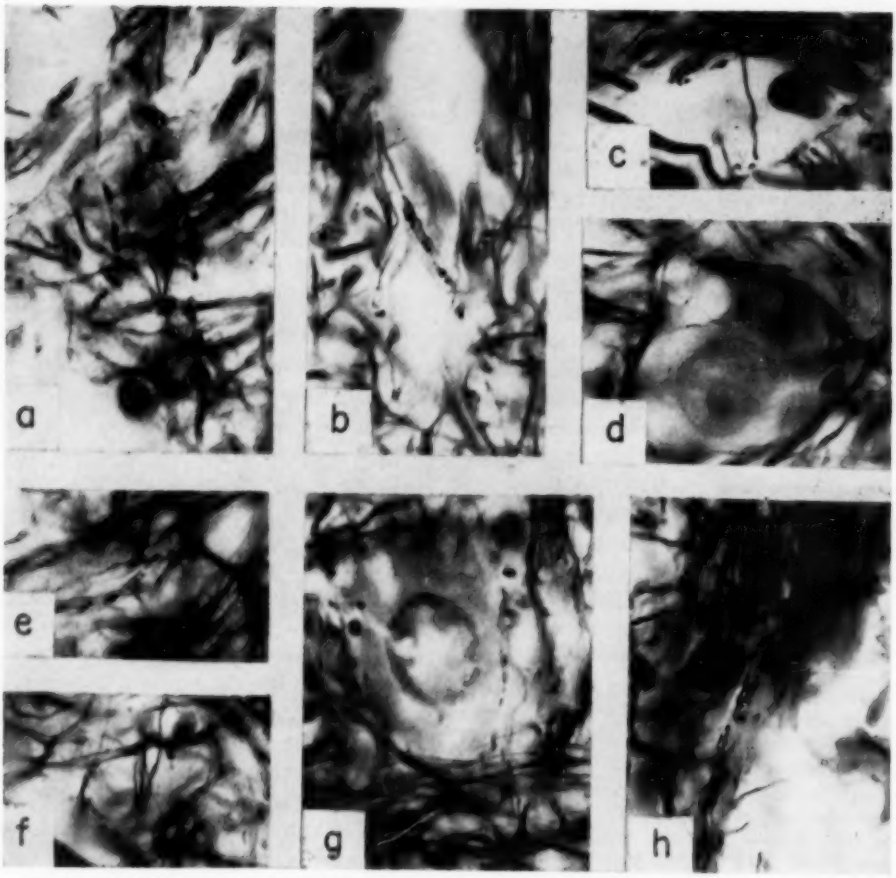

Fig. 1.—Photomicrographs of silver-impregnated sections (Glees method) from the reticular formation of the cat, showing appearance of terminal degeneration and degenerating fibers following lesions of the spinal cord. Reduced to 90% of mag. × 1200.

(*a*) Degenerating spinoreticular fibers ascending through the nucleus reticularis pontis caudalis (Cat Sp. C. L. 15; cf. Fig. 4).

(*b*) Preterminal degenerating fiber in the same nucleus (Cat Sp. C. L. 20, cf. Fig. 4).

(*c*) Terminal degenerating fiber in the nucleus reticularis pontis oralis (Cat Sp. C. L. 26; cf. Fig. 2).

(*d*) Preterminal degenerating fiber in the nucleus subcaeruleus (Cat Sp. C. L. 26).

(*e*) and (*f*) Terminal degenerating fibers with boutons in the nucleus subcaeruleus and the nucleus reticularis ventralis, respectively (Cat Sp. C. L. 26; cf. Fig. 2).

(*g*) and (*h*) Terminal degenerating fibers establishing contact with cell body (*g*) and cell process (*h*) in the nucleus reticularis gigantocellularis (Cat Sp. C. L. 20; cf. Fig. 4).

Course and Termination of Spinoreticular Fibers

Since it was of particular interest to determine the exact terminal distribution of spinal afferents to the reticular formation, we have attempted to indicate their terminal regions with reference to the various groups of reticular neurons which can be outlined on a cytoarchitectonic basis. The grouping of cells has been made according to the principles used by Meessen and Olszewski [25] in their atlas of the brain stem of the rabbit. There are only minor differences between the cat and the rabbit with regard to these delimitations. In order to identify the various groups in the horizontal silver-impregnated sections used in this study, comparisons have been made with similarly cut

Nissl-stained sections and with a series of drawings of transverse Nissl-stained sections of the brain stem of the cat, published elsewhere.[9] We have, however, ignored some of the minor, and in our opinion more equivocal, subdivisions distinguished by Meessen and Olszewski. The nuclear groups recognized and their approximate borders (broken lines) are seen from Figure 2. The density of dots in this Figure serves to give an impression of the intensity of terminal degeneration in different regions of the reticular formation. Terminal degeneration occurring in other brain stem structures, such as the inferior olive, the lateral reticular nucleus, and others, will not be considered here.

In all experimental animals in which terminal degeneration was found in the reticular formation its distribution was similar. It will be sufficient, therefore, to present one case which shows the terminal regions, and to mention more briefly other cases which give information on the course of the spinoreticular fibers within the cord, of their levels of origin, and of quantitative differences with regard to the degeneration in the reticular formation.

CAT Sp. C. L. 26, killed after six days (Figs. 1, 2, and 3).

Lesion.—The ventral and most of the right lateral funiculus were transected at the level of C 3 (Fig. 2, below). There is some damage to the right ventral horn.

Course of Fibers.—In the horizontal silver-stained sections degenerating fibers are found in large numbers ventrolateral to the right lateral reticular nucleus (*N. r. l.*, drawings *8-18*, Fig. 2). These fibers can be followed rostrad along the lateral surface of the medulla. Where it takes off in a dorsal direction, the ventral spinocerebellar tract is seen to be completely degenerated. Many fibers are seen to leave the superficially situated bundle in the medulla and to enter the lateral reticular nucleus, as described previously.[9] Some degenerating fibers penetrate the nucleus in a lateromedial direction and enter the reticular formation medial to the nucleus, particularly at caudal medullary levels. Some of these fibers may be collaterals of ascending fibers, while others, on account of their relatively large caliber, must be assumed to be parent fibers leaving the main bundle. Scattered degenerating fibers of the same type are found on the left.

Other ascending degenerating fibers enter the medullary reticular formation medial to the right lateral reticular nucleus (Fig. 2, drawings *11-21*). These fibers can be followed in gradually decreasing numbers in a rostral direction throughout the medullary and pontine reticular formation. In the rostral part of the latter they become scanty. Degenerating medium-sized and finer fibers are also seen to run transversely or slightly obliquely in the right, as well as in the left, medullary and pontine reticular formation. Since fibers with this direction are seen to cross the raphe, particularly at the level of the abducent nerve, they are taken to represent fibers crossing from the right to the left. While in the pontine reticular formation the number of degenerating ascending and transversely running fibers is approximately equal on the two sides, in the medulla they are far more abundant on the right (side of the lesion) than on the left.

Sites of termination.—In the medullary reticular formation terminal degeneration is far more abundant on the right side than on the left, particularly at caudal levels. On both sides it is more intense ventrally than dorsally, as seen from the dotting in the drawings in Figure 2. Maximum of degeneration is found in the reticular formation lateral and dorsorostral to the inferior olive. In terms of cytoarchitectonic subdivisions, the degeneration is found in the nucleus reticularis ventralis (*R. v.*, drawings *11-21*, Fig. 2), in the nucleus reticularis lateralis of Meessen and Olszewski (*R. l.*, drawing *8*, Fig. 2) and in the nucleus reticularis gigantocellularis (*R. gc.*, drawings *8-27*, Fig. 2). In the last nucleus there is a clear-cut difference between its ventrocaudal region, which contains a considerable number of degenerating terminal fibers, and its dorsal and rostral regions, where only few such fibers can be found. In the nucleus reticularis parvicellularis (*R. pc.*, Fig. 2) degenerating terminal fibers are very scanty. Several of the giant cells of the nucleus reticularis gigantocellularis show terminal fibers attached to their surface (Fig. 3), thus indicating synaptical contact with spinoreticular fibers. A particular small-celled group (*x* in drawing *8*, Fig. 2), situated immediately ventral to the facial nucleus, shows clear-cut terminal degeneration. Whether its afferents enter it from the medial or the lateral side could not be established. This small group is not seen in the map of Meessen and Olszewski.[8] In Nissl-stained sections of the cat it appears as a particular lateral prolongation of the nucleus reticularis lateralis (of Meessen and Olszewski).

In the pontine reticular formation convincing quantitative differences between the two sides with regard to terminal degenerating fibers cannot be established. The cytoarchitectonic groups showing degeneration in the pons are the nucleus reticularis

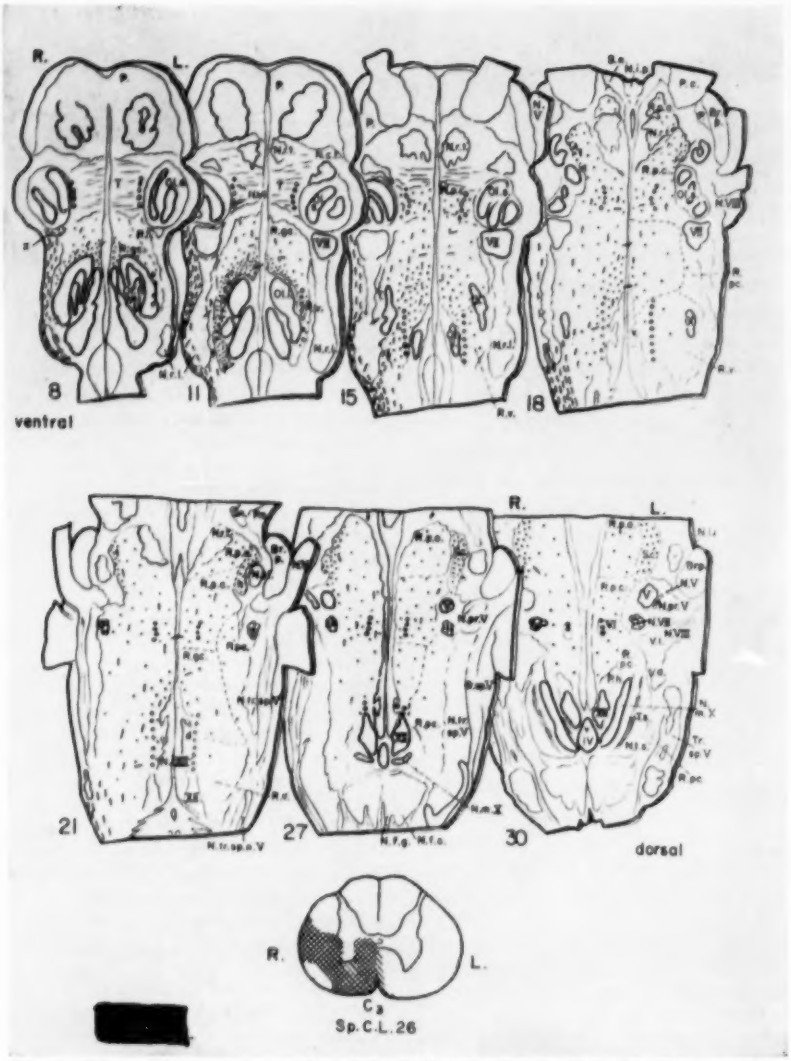

Fig. 2.—Diagrammatic representation of the findings in Cat Sp. C. L. 26. Below, a diagram of the lesion in the spinal cord (cross hatching). Above, a series of drawings of horizontal sections through the pons and medulla made by means of a projection apparatus. The numeral below each drawing refers to the group of 15 consecutive sections from which the section reproduced has been taken. The numbering gives an impression of the relative intervals between the sections reproduced. Degenerating coarser fibers are shown as wavy lines. Distribution of terminal degeneration in the noncerebellar projecting part of the reticular formation is indicated by dots. The density of the dotting gives an impression of the relative intensity of degeneration in various regions. Broken lines indicate the approximate borders between cellular groups distinguished on a cytoarchitectonic basis in accordance with Meessen and Olszewski. Terminal degeneration occurring in other nuclei, such as the inferior olivary nucleus and the lateral reticular nucleus, is not mapped.

Abbreviations are as follows: *a, d, v,* accessory, dorsal and ventral groups, respectively, of the paramedian reticular nucleus; *Br. p.*, brachium pontis; *h*, Group h of Meessen and Olszewski; *L.*, left; *N. c. t.*, nuclei of trapezoid body; *N. f. c.*, nucleus cuneatus; *N. f. g.*, nucleus gracilis; *N. i. p.*, nucleus interpeduncularis; *N. l. l.*, nuclei of lateral lemniscus; *N. m. X*, dorsal motor vagus nucleus; *N. pr. V*, principal trigeminal sensory nucleus; *N. r. l.*, lateral reticular nucleus (nucleus of lateral funiculus); *N. r. t.*, nucleus reticularis tegmenti pontis; *N. tr. sp. V*, nucleus of spinal trigeminal tract; *N. t. s.*, nucleus of solitary tract; *N. V, VI, VII, VIII, XII*, root fibers of cranial nerves specified; *Ol. i.*, inferior olive; *Ol. s.*, superior olive; *P.*, pontine nuclei; *P. c.*, cerebral peduncle; *P. h.*, nucleus praepositus hypoglossi; *R.*, right; *R. gc.*, nucleus reticularis gigantocellularis; *R. l.*, nucleus reticularis lateralis (of Meessen and Olszewski); *R. pc.*, nucleus reticularis parvicellularis; *R. p. c.*, nucleus reticularis pontis caudalis; *R. p. o.*, nucleus reticularis pontis oralis; *R. v.*, nucleus reticularis ventralis; *S. c.*, nucleus subcaeruleus; *S. n.*, substantia nigra; *T.*, trapezoid body; *Ts.*, solitary tract; *Tr. sp. V*, spinal trigeminal tract; *V. d.*, descending vestibular nucleus; *V. l.*, lateral vestibular nucleus; *x*, cell group x; *V, VI, VII, X, XII*, motor nuclei of cranial nerves.

Fig. 3.—Drawings of a giant cell and a large cell from the nucleus reticularis gigantocellularis in Cat Sp. C. L. 26, showing degenerating terminal fibers (on the giant cell also possibly a *bouton en passage*, arrow) attached to the cell surface. Below the giant cell a preterminal degenerating fiber (cf. Fig. 1*g* and *h*).

pontis caudalis and nucleus reticularis pontis oralis. (*R. p. c.* and *R. p. o.*, Fig. 2), and a fairly characteristic cell group in the rostral pons, situated medial to the nucleus of the lateral lemniscus, laterodorsal to the reticularis pontis oralis, ventral to the nucleus of the locus caeruleus, and rostral to the motor trigeminal nucleus. From its position this nucleus is taken to represent the nucleus subcaeruleus. (It appears to correspond to the nucleus caeruleus pars *a* of Meessen and Olszewski,[35] to the nucleus ventralis Brachii of Winkler and Potter.[61] In the map of the cat's reticular formation, published elsewhere (Brodal[9]), it is seen in Drawings 4 and 5, ventral to the nucleus caeruleus, but is not labeled.) This nucleus subcaeruleus, judging from the intensity of terminal degeneration within it, receives a larger contingent of spinal afferents than the caudal and oral pontine reticular nuclei. This degeneration extends also caudally to include a small group situated medial to the motor trigeminal nucleus, labeled *h* by Meessen and Olszewski (Drawing 6 in Figure 1, Brodal[9]). Within the nucleus reticularis pontis oralis and nucleus reticularis pontis caudalis, there appears to be a little more degeneration at the level of the abducent nerve than at more rostral levels, but the difference is not very marked.

In the mesencephalic reticular formation very scattered degenerating terminal fibers are seen. Since the mesencephalon was cut separately in transverse sections, it is not included in the drawings of Figure 2.

A distribution of terminal degeneration and a course of ascending degenerating fibers identical with that in Cat Sp. C. L. 26, described above, was found in Cats Sp. C. L. 21b and R. 103 (killed after five and four days, lesions at the level of C 1 and C 3, respectively). In both these animals (Fig. 4) the lesion involved one lateral funiculus but spared the ventral funiculus. Particularly illuminating concerning the course taken by the spinoreticular fibers is Cat R. 113 (killed

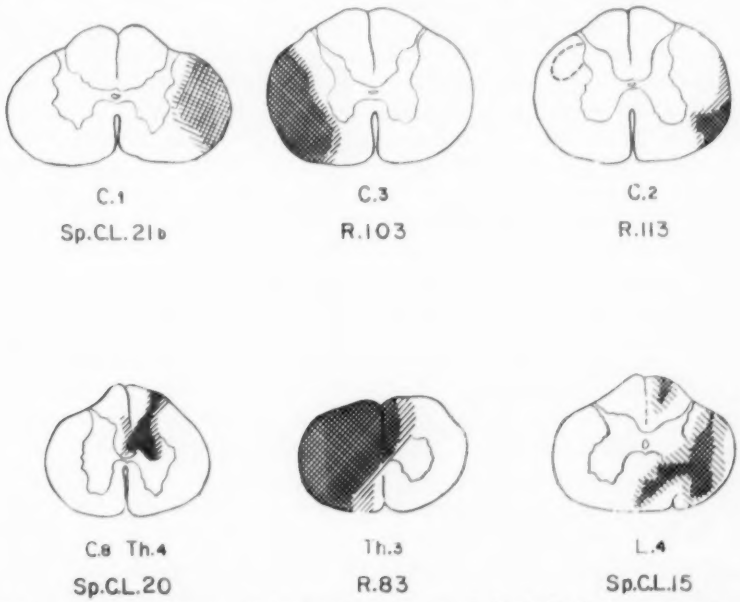

Fig. 4.—Diagram showing the level and the extent of the lesion in some cases in which terminal degeneration is present in the reticular formation. The intensity of terminal degeneration differs in various cases (cf. text), but its distribution is similar to that shown in Figure 1.

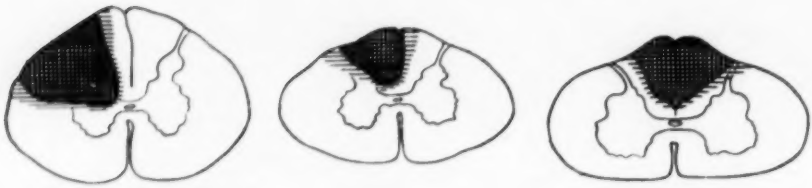

Fig. 5.—Diagram showing the level and the extent of the lesion in some cases in which terminal degeneration is not found in the reticular formation. Compare text.

after four days), in which the lesion involves only the ventral part of the lateral funiculus. Terminal degeneration is present in the same regions as in Cat Sp. C. L. 26 (Fig. 2) and is almost as marked. When taken together, these cases, as well as others, not described, show that a majority, if not all, of the reticulospinal fibers ascend in the ventral part of the lateral funiculus. Since we have no case with a lesion restricted to the ventral funiculus, we cannot exclude the possibility that some reticulospinal fibers ascend here, but their number must be rather modest. That no reticulospinal fibers ascend in the dorsal funiculi or in the dorsal part of the lateral funiculus is learned from cases like those shown in Figure 5, as well as others with similar lesions. No degeneration of reticulospinal fibers and no terminal degeneration in the reticular formation was found in any of these animals.

Following lesions at thoracic and lumbar levels involving the lateral funiculus, reticulospinal fibers degenerate and terminal denegeration is found in the reticular formation. Cat R. 83 (killed after four days), with a lesion at T 3, and Cat Sp. C. L. 15 (killed after five days), with a lesion at L 4, are shown as examples in Figure 4. Terminal degeneration is found in the same regions as that described following cervical lesions. The degeneration is less intense, but the regional differences among the various reticular nuclear groups are similar to those seen following high cervical lesions.

The cases reported above make clear that spinoreticular fibers come from levels of the cord as far caudal as the lumbar segments. That the thoracic segments contribute to the spinoreticular projection is learned from the findings in Cat Sp. C. L. 20 (killed after five days), since a destruction of the dorsal horn from C 8 to T 4 (Fig. 4) is followed by clear-cut terminal degeneration, as in the cases just referred to. In this case the maximum of changes in the medulla is found on the side contralateral to the lesion, thus indicating that the majority of reticulospinal fibers cross in the medulla before ascending in the lateral funiculus.

The similar distribution of terminal degeneration following lesions at different levels of the cord shows that there is no obvious somatotopical arrangement within the terminal regions of the spinoreticular fibers. It is learned from our findings that while spinoreticular fibers reach large territories of the medullary and pontine reticular formation, certain regions are much more amply supplied with such fibers than others. To some extent the maximal terminal regions can be correlated with particular reticular cell groups. In the medullary reticular formation the bulk of the fibers terminate in the caudal and ventral regions of the nucleus reticularis gigantocellularis, in the nucleus reticularis ventralis, and in the nucleus reticularis lateralis (of Meessen and Olszewski), including a small-cell group situated at the ventral border of the facial

nucleus (*x*, Fig. 2). As judged by the intensity of terminal degeneration, the nucleus subcearuleus is the most important terminal station within the pontine reticular formation.

It appears from our findings that the spinoreticular fibers to the pons ascend within the reticular formation (Fig. 2). On their way they pass through the medullary reticular formation, together with fibers which end here, particularly in the nucleus reticularis gigantocellularis. These fibers are to be considered as direct medial reticulospinal fibers, since they enter the reticular formation medial to the lateral reticular nucleus (nucleus of the lateral funiculus). Other fibers to the medullary reticular formation enter it from the degenerating fiber bundles ascending lateral to this nucleus. These fibers are, presumably in part, collaterals of fibers, continuing to higher levels, but the large caliber of many of them indicates that there are also direct (lateral) spinoreticular fibers among them.

Comment

Terminal Degeneration in the Reticular Formation.—As described above, only degenerating fibers of the finest type have been considered as indicating the region of termination of transected spinal afferent fibers to the reticular formation. The appearance of these fibers is characteristic, and similar to the pictures of degenerating terminal fibers observed in numerous other nuclei. This, as well as the absence of fibers of this type in normal control material, and in cases with lesions sparing the ventrolateral funiculus, makes us feel certain that the areas found to contain degenerating terminal fibers are true terminal stations of spinoreticular fibers. Since possibly degenerating terminal boutons have been left out of consideration, relatively little information has been obtained with regard to the manner in which the fibers establish synaptical contact with cells of the reticular formation. The occasional finding of a degenerating bouton (identified by its being connected with a degenerating terminal fiber) on a cell body or a cell process makes clear that contacts are established via terminal boutons. Whether there may be other types of endings as well remains, however, an open question. Nor is it possible to decide whether the spinal afferents terminate on cells of all types. Synaptical contacts with large and giant cells have, however, been observed (Fig. 3).

On account of the enormous number of fibers which traverse the reticular formation in all directions, the degenerating terminal fibers do not stand out as clearly as they usually do in more well-circumscribed nuclei, where the cells are more closely packed together. This makes the search for terminal degeneration in the reticular formation (which has to be done under oil immersion) a very laborious task and contributes significantly to make quantitative estimates of degenerating terminal fibers difficult. Only marked differences in the number of such fibers can, therefore, be recognized. Variations in the degree of impregnation, which appear to be unavoidable in all silver impregnation methods, contribute to these difficulties, particularly with regard to comparisons of different series. In our study we have, therefore, only taken into account quantitative differences which are clear-cut, and which have been found with consistency in more than one series. It is well possible, however, that there may be minor regional variations with regard to the intensity of degeneration which have escaped recognition in our study.

Course and Termination of Spinoreticular Fibers.—Our findings concerning the course of spinoreticular afferents within the spinal cord are in agreement with those made by most previous authors. It is clear that the vast majority of these fibers ascend in the lateral funiculus, chiefly its ventral part. Since we have no cases with lesions restricted to the ventral funiculus, we cannot exclude the possibility that some fibers ascend here as well. Their number appears to be scanty, however, since the inclusion in the lesion of

the ventral funiculus, in addition to the lateral, seems to make no difference with regard to the intensity of terminal degeneration in the reticular formation. Like most previous authors, we did not find afferents to the reticular formation ascending in the dorsal funiculi. Nor were we able to confirm the view held by some [7,15,37] that the dorsal spirocerebellar tract gives off collaterals to the reticular formation.

In addition to lateral spinoreticular fibers, presumably in part collaterals from the spinothalamic tract, our material confirms the existence of a medially coursing (direct) spinoreticular tract, as described by previous authors.[6,26,28,30] Its fibers ascend medial to the lateral reticular nucleus and can be followed through the medullary and pontine reticular formation (Fig. 2). While the pontine reticular formation appears to be supplied exclusively via the medial tract, it is difficult to decide to which extent this terminates in the medulla. It appears, however, that lateral fibers and the collaterals from the spinothalamic tract reach chiefly the nucleus reticularis ventralis and the nucleus reticularis lateralis, while the nucleus reticularis gigantocellularis is chiefly supplied by medially coursing fibers. To some extent these certainly end also in the nuclei reticularis lateralis and ventralis.

As described above, spinoreticular fibers may be traced to practically all regions of the medullary and pontine reticular formation. However, some nuclear groups receive only a very modest number of such fibers, while others have an ample supply. The maximal medullary area of termination of spinoreticular fibers determined in the present study is the same as that described by previous workers, using the Marchi method, namely, the region dorsal and lateral to the inferior olive. Likewise, we have confirmed the observation that there are fibers to the pontine reticular formation at the level of the abducent nerve. However, the method of terminal degeneration makes it possible to obtain more precise information on the terminal areas. With regard to this point our findings largely agree with those made by others using similar methods. Thus we are in agreement with Johnson [21] and Mehler, Feferman, and Nauta [26] when they state that (in the cat and monkey, respectively) spinoreticular fibers end in the nucleus reticularis ventralis, nucleus reticularis lateralis, and nucleus reticularis gigantocellularis in the medulla, and in the nucleus reticularis pontis caudalis. Like Johnson,[21] we found fibers to the nucleus reticularis pontis oralis, while Mehler et al.[26] did not observe them in the monkey. We are in agreement with these authors that very few fibers end in the nucleus reticularis parvicellularis. As in the monkey,[26] there are in the cat spinal afferents to the nucleus subcaeruleus (which apparently have been missed by the workers using the Marchi method). If there are some fibers ending in the mesencephalic reticular formation, their number must be extremely small. The small group labeled *x* in Figure 2 may correspond to what Mehler et al.[26] refer to as the pars ventralis of the facial nucleus, to which they traced spinoreticular fibers.†

Our observation that certain regions of the reticular formation receive more abundant spinal afferents than others is of particular interest, since there are also regional differences with regard to the terminal distribution of corticoreticular fibers [33] and with regard to the sites of origin of reticulospinal fibers [38] and of fibers ascending to higher levels.[12] The findings made in the present study, therefore, furnish an additional argument against the conception that the reticular formation is diffusely organized, and support the views derived from cytoarchitectonic studies that the reticular formation may be

† Like Johnson,[21] we have found spinal afferents to the nucleus of the spinal trigeminal tract. There are also afferents to the nucleus of the solitary tract. These findings have been reported on elsewhere.[42] We have confirmed the existence of spinal afferents to the nucleus of the raphe.[39] Since at least some cells of this nucleus have long ascending axons,[12] the nucleus of the raphe appears to be functionally closely related to certain other regions of the reticular formation, just as from a structural point of view it may be considered a reticular nucleus.

considered as made up of particular nuclei, being different functionally as well as structurally. However, the existence of regional differences within the nucleus reticularis gigantocellularis with regard to its richness in spinal afferents, like other observations,[9,12,33,38] make clear that this nuclear group, as well as others, is scarcely functionally uniform throughout.

Functional Correlations

Our experimental material makes clear that the reticular formation receives an important contingent of direct fibers from the spinal cord, even from its lowest levels. In addition, certain areas of the reticular formation are reached by collaterals from spinothalamic and other fibers ascending in the ventrolateral funiculus of the cord. While the functional role of the spinoreticular fibers cannot be decided from anatomical studies, anatomical data may, nevertheless, give some clues of interest for functional problems. Thus it is striking that the medullary terminal area of reticulospinal fibers coincides almost completely with the region of the medullary reticular formation, which, according to our previous study,[12] is particularly rich in cells with long axons ascending to higher levels of the brain stem, above the mesencephalon. This regional correspondence makes it appear extremely likely that this part of the reticular formation (particularly the ventrocaudal part of the nucleus reticularis gigantocellularis and the ventral regions of the nucleus reticularis ventralis and nucleus reticularis lateralis) functions as a station in a pathway from the spinal cord to certain nuclei of the thalamus and higher-level structures.‡ The assumption may, therefore, be ventured that the direct spinoreticular fibers are important in influencing the ascending activating system of the brain stem, and that the activation following stimulation of spinal nerves does not occur exclusively, perhaps not even preponderantly, by way of collaterals from spinothalamic fibers. (This subject has been discussed more fully elsewhere.[9])

We have shown in a previous study[12] that, in addition to the medullary region discussed above, there is another region of reticular formation which is particularly rich in cells having long ascending axons: the caudal part of the nucleus reticularis pontis caudalis, at the level of the abducent nerve. However, although receiving spinoreticular fibers, this region does not appear to be particularly well supplied with such afferents. This makes it likely, as we have suggested previously,[12] that the rostrally projecting region at the level of the abducent nerve is relatively little concerned in the activation of the ascending system by spinal impulses, and that it may serve as an important recipient of afferent impulses of other origin, for example, acoustic and trigeminal. Roger, Rossi, and Zirondoli[32] have shown that in the *encéphale isolé* cat bilateral destruction of the Gasserian ganglion is followed by synchronization of the EEG, and they assume that the trigeminal impulses are particularly important for maintaining the tonic activity within the ascending activating system. While the detailed anatomy of the distribution of trigeminal sensory impulses to the reticular formation is not yet known, the situation of the rostrally projecting neurons at the pontine level makes it appear likely that they receive an ample supply of trigeminal impulses. It may be suggested, therefore, that the two aggregations of rostrally projecting neurons within the reticular formation are related each to one of the two groups of afferent impulses which have been shown in physiological studies to be most important for maintaining the tonic activity of the reticular formation, namely, spinal and trigeminal.

This hypothesis will have to be tested by physiological experiments aiming particu-

‡ It is interesting to notice that there are even some direct spinothalamic fibers which terminate in the intralaminar and reticular thalamic nuclei, as shown by Getz,[16] Mehler et al.,[28] and other authors. These fibers, although not very numerous, like the spinoreticulothalamic pathway discussed here, may presumably also play a role in the ascending activating system.

larly at deciding the sites of maximal influxes of spinal and trigeminal impulses, respectively, to the reticular formation. Even if it has repeatedly been observed (Starzl et al.[36] and other authors) that, following stimulation of spinal nerves, potentials may be led off with macroelectrodes from almost any part of the reticular formation, this does not invalidate the assumption set forth here. The potentials recorded with macroelectrodes, and having a long latency and a long duration, have to be considered as resulting from the activation of a large population of reticular neurons rather than the responses of the cells activated directly by the spinal impulses. However, the observation that under barbiturate anesthesia stimulation of the saphenous nerve gives rise to potentials in the medulla oblongata localized chiefly lateral and dorsolateral to the inferior olive[5] may deserve mention, since barbiturate anesthesia is known to depress the propagation of impulses within the reticular formation.[2,17]

In recent years many workers have recorded impulses to the reticular formation by means of microelectrodes (Amassian,[1] von Baumgarten,[3] Cooper,[16] Machne,[24] Scheibels,[35] and their associates, and others). However, these studies did not have as their purpose to determine the maximal regions of influx of afferent impulses of a particular type. This would require also a determination of latencies, in order to decide whether the units recorded from can be considered as activated directly by the spinal impulses. A systematic study of this type might yield interesting results. That reticular units responding to stimulation of spinal nerves have been found throughout the length of the reticular formation is easily compatible with the termination of spinoreticular fibers demonstrated in the present study. The convergence of spinal and cortical impulses on the same units[1,3,35] is also in complete agreement with anatomical data, since we have traced corticoreticular fibers to all levels of the reticular formation,[33] although these fibers, like the spinoreticular, have their preferential sites of termination. These largely coincide with the regions giving off reticulospinal fibers.[38]

We are unable to offer any functional explanation of the fact that the nucleus subcaeruleus receives a considerable number of spinoreticular fibers. The vicinity of this nucleus to the nucleus caeruleus, which appears to be part of the pneumotaxic center,[4] invites speculations as to whether the nucleus subcaeruleus may play a role as an "afferent center" in the regulation of respiration.

So far we have considered the role of the spinoreticular fibers as links in pathways from the spinal cord to the thalamus and other high-level structures. It appears, however, reasonable that these fibers may have other tasks as well. They may, for example, form a link in feed-back circuits between the spinal cord and the reticular formation. The fact that some spinoreticular fibers terminate in regions which send a majority of their fibers to the spinal cord (see Torvik and Brodal[38] for particulars) makes this a likely assumption. Support for this view is derived from the observation that spinoreticular fibers have been seen to establish synaptical contact with giant cells in the nucleus reticularis gigantocellularis, since no giant cells in this nucleus have been found to give off ascending axons,[12] while most, and probably all, of them project to the spinal cord.[38] It is of interest to note that regions of the reticular formation outlined in physiological studies as facilitatory, as well as inhibitory, receive spinoreticular fibers, and that such fibers are derived even from lumbar levels of the cord. It may be of functional importance that the inhibitory region appears to be more amply supplied with spinal afferents than the facilitatory region. Similarly, the inspiratory and the depressor regions appear to receive more spinal afferents than the expiratory and pressor regions, respectively.

The anatomical data brought forward in this study cannot be fully correlated with known physiological studies. However, they may serve as useful guides when in the future the reticular formation will have to be studied more minutely with reference to

possible functional differences between its various subdivisions. Like our previous studies on the termination of corticoreticular fibers,[33] and on the sites of origin of long ascending [12] and descending fibers from the reticular formation,[38] the findings made in the present work bear evidence that the reticular formation is not diffusely organized. As discussed at some length elsewhere,[9] the reticular formation may be subdivided into various regions, which have their particular structure and their particular fiber connections, even if the borders between these regions are not sharp. Such anatomical data provide weighty arguments for the view that neither in a physiological sense is the reticular formation diffusely organized.

Summary

Following lesions of the spinal cord in cats, the course and terminal distribution of fibers ascending to the reticular formation have been studied in silver-impregnated sections (Glees method). The reticular nuclei projecting onto the cerebellum, studied previously, have not been considered. The occurrence of terminal degenerating fibers is taken to indicate the areas of termination of spinoreticular fibers.

The majority of the spinoreticular fibers ascend in the ventral part of the lateral funiculus of the cord. In the medulla some of them join the spinothalamic tract in its ascending course and then bend medially, together with collaterals from fibers ascending further. Other spinoreticular fibers reach the reticular formation directly along a medial route. The latter fibers can be traced rostralward in gradually decreasing numbers throughout the medulla and pons.

The fibers to the medullary reticular formation are distributed chiefly homolaterally (with respect to their course in the cord); those to the pontine reticular formation, bilaterally.

A large number of spinoreticular fibers terminate in the medulla rostrodorsal and lateral to the inferior olive, i. e., in the caudal and ventral parts of the nucleus reticularis gigantocellularis, the nucleus reticularis ventralis, and the nucleus reticularis lateralis (of Meessen and Olszewski), including a particular small part of it situated ventral to the facial nucleus. In the pons the terminal areas comprise the nucleus reticularis pontis oralis and nucleus reticularis pontis caudalis, possibly with some overweight in the caudal part of the latter, but the densest region of termination is the nucleus subcaeruleus.

The findings support the general conclusion reached in studies of other fiber connections of the reticular formation, that the reticular formation is not diffusely organized. Some functional correlations are attempted. Since a large number of the spinoreticular fibers to the medullary reticular formation end in regions giving origin to long ascending fibers, it is suggested that there exists a fairly direct pathway from the spinal cord to the higher levels of the ascending activating system. In addition, the terminal distribution of spinoreticular fibers indicates that they may serve as links in feed-back circuits between the spinal cord and the reticular formation.

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Hypothermia and Cerebral Vascular Lesions

II. Experimental Middle Cerebral Artery Interruption Followed by Induction of Hypothermia

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Introduction

In Part I of this study, it was postulated that the process of cerebral infarction would be modified or prevented if body temperature were reduced at the time of arterial occlusion.[1] To test this hypothesis, the middle cerebral artery of the dog was interrupted at normal body temperature and during hypothermia. Each normothermic dog developed a cerebral infarct. When interruption of the artery occurred at 22-24 C, either no infarct developed or lesions were found which were small in size and restricted to relatively "silent areas." It was concluded, therefore, that hypothermia protects against cerebral infarction in the dog.

The present set of experiments was undertaken to ascertain whether hypothermia would have a similar effect if the artery were interrupted at normal body temperature and then hypothermia were induced. It was hoped that such a study would provide data and, perhaps, a therapeutic technique which would be of value in the consideration of cerebral vascular disease in man.

The basic plan of study incorporated the following sequence of events: (1) middle cerebral artery interruption; (2) a waiting period, designated as the "delay time," which was varied by experimental design; (3) induction of hypothermia to 24 C; (4) maintenance of a body temperature of 24 C or less for one hour, and (5) rewarming to normothermic levels. The data suggest that benefit may be derived from a reduction of body temperature if the induction of hypothermia is begun within 15 minutes following the arterial interruption and a 24 C level is attained within a total elapsed time of 90 minutes.

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Methods

Forty mongrel dogs, weighing between 10.4 and 22.0 kg. and unselected as to age and sex, were used in this investigation.

Twenty-four hours before each experiment, the dogs were given 600,000 units of long-acting benzathine penicillin G (U. S. P.), intramuscularly, and 0.4 gm. of diphenylhydantoin sodium, orally. The diphenylhydantoin sodium was administered daily through the fifth postoperative day in order to suppress convulsions.

Anesthesia was achieved with intravenous pentobarbital sodium, 30 mg/kg. Body hair was removed with clippers, and the dogs were intubated with a cuffed No. 38 F. endotracheal catheter. The catheter was attached to an automatic positive-negative pressure closed-system respirator,* which delivered 100% oxygen at a rate of 24 respirations per minute. The positive pressure was adjusted between 7 and 11 mm. Hg and the negative pressure between 1 and 4 mm. Hg, in order to maintain a tidal exchange of 200-400 ml. A thermistor was inserted 200 mm. into the esophagus for the recording of body temperature.

With the dog in the right lateral recumbent position, a left subtemporal craniectomy was performed, using aseptic technique. The dura mater was incised, and the pyriform lobe was gently retracted to expose the middle cerebral artery. Since past experience had indicated that segmental resection

* Designed by Dr. D. A. Holaday and constructed by the Metal Model Shop of the Naval Medical Research Institute, with parts supplied by the Ohio Chemical & Surgical Equipment Company.

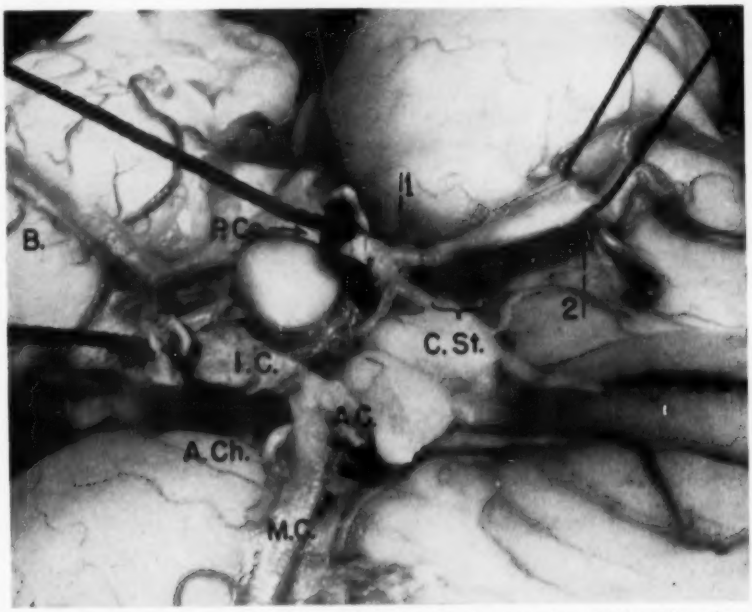

Fig. 1.—Basal view of a dog brain demonstrating the vascular relationships about the middle cerebral artery. *M. C.*, middle cerebral artery; *A. Ch.*, anterior choroidal artery; *C. St.*, central (striatal) arteries; *A. C.*, anterior cerebral artery; *I. C.*, internal carotid artery; *P. Co.*, posterior communicating artery; *B.*, basilar artery; arrow *1*, origin of the middle cerebral artery; arrow *2*, first major cortical bifurcation of the middle cerebral artery. From Part I, published in the *Journal of Neurosurgery* (13:244-255, 1956), reproduced by permission of Charles C Thomas, Publisher, Springfield, Ill.

of the middle cerebral artery produced the most consistent and extensive lesions, this procedure was utilized exclusively in these experiments to effect the vascular interruption. The artery was resected from its origin to the first major cortical bifurcation. This included coagulation and section of each central (striatal) branch and the anterior choroidal artery, which, in the dog, arises from this segment of the middle cerebral artery. The section of artery removed corresponds to that segment indicated between arrows *1* and *2* in Figure 1. The dura mater was approximated over strips of absorbable gelatin sponge U. S. P., and the incision was closed in layers, utilizing stainless-steel screening to cover the craniectomy defect.

Hypothermia was induced by immersion to the shoulders in ice water. Initiation of hypothermia was begun at variable periods, designated the delay time (DT), following initial occlusion of the middle cerebral artery. The delay times ranged from immediate application of the ice, DT 0, to 2 hours, DT 120. When the body temperature had reached 25 C, the ice was removed. Body temperature usually decreased an additional 1-4 degrees (C). The animal was kept at a body temperature of 24 C or less for a period of one hour. Then the dog was rewarmed in a water bath in which the temperature was kept 10 degrees (C) higher than that of the dog, until a body temperature of 35 C was reached. Rewarming was then discontinued, and the animal was allowed spontaneously to regain the normothermic state. All animals were observed for 18-22 days. They were then reanesthetized and killed by formalin perfusion. The brains were removed and studied grossly and microscopically.

Occlusion of the middle cerebral artery in the normothermic dog produces a triad of clinically detectable manifestations. These are (1) ipsilateral forced circling movements, (2) a contralateral hemiparesis, and (3) a contralateral temporal homonymous visual field defect. A visual field defect was said to be present when no reaction was obtained in response to the examiner's finger movements or when the animal bumped into objects placed in the suspected field of vision. The animals were examined daily, and the presence or absence of the above signs was recorded. No attempt was made to evaluate the clinical signs during the first 48 hours postoperatively, since it was difficult to differentiate between the transient signs due to operative handling and those due to

permanent brain damage. The subsequent course was divided into five periods, as follows:

Period 1: 3 to 5 postoperative days
Period 2: 6 to 8 postoperative days
Period 3: 9 to 11 postoperative days
Period 4: 12 to 14 postoperative days
Period 5: 15th day to day of killing

A neurological score was computed for each animal. One point was given for each of the clinical signs, when present, and this was multiplied by the number of postoperative periods during which it persisted. Thus, the maximum score was 15.

The dogs were distributed between two groups: (1) 10 dogs in which the left middle cerebral artery was segmentally resected at normal body temperature, the normothermic controls, and (2) 27 dogs in which the left middle cerebral artery was resected at normal body temperature, followed by the induction of hypothermia at variable delay times. Three additional dogs died during hypothermia, owing to cardiac arrest; they were not included in the evaluation of the experimental results of this study.

Results

1. *Segmental Resection of the Middle Cerebral Artery at Normal Body Temperature.*—In order to establish control values, the left middle cerebral artery was resected from its origin to the first major cortical bifurcation in 10 normothermic dogs. The results are listed in Table 1.

All 10 dogs developed cerebral infarcts. A representative illustration of the lesion is shown in Figure 2. The infarcted area included destruction of the basal ganglia, internal capsule, thalamus, hypothalamus, visual pathways, and portions of the overlying frontoparietotemporal cortex on the left side. Eight of the ten dogs had such extensive lesions; they manifested correspondingly severe neurological signs, scores of 12-15. Two animals developed less extensive pathology; they exhibited less severe clinical signs, scores of 10 and 6, respectively.

2. *Resection of the Middle Cerebral Artery Followed by Hypothermia.*—The left middle cerebral artery of 27 dogs was segmentally resected at normal body temperature. Following initial interruption of the artery, hypothermia was induced, as indicated by the "delay times" listed in Table 2. The "delay times" ranged from immediate application of the ice, DT 0, to a delay of 2 hours, DT 120. The animals' temperatures were reduced to 24 C, and hypothermia was maintained at or below this level for a period of one hour. During this hour the temperature fell another 1-4 degrees (C), resulting in a mean low temperature of 21.9 C. They were then rewarmed, requiring an average 108 minutes to return to normothermic levels.

The results were tabulated in Table 2 and plotted graphically in Figure 3. In Figure 3, the delay time and the total elapsed time from interruption of the artery to the

TABLE 1.—*Segmental Resection of the Middle Cerebral Artery at Normal Body Temperature*

Dog No.	Results	Neurological Score
2801	Infarction putamen, globus pallidus, caudate n., amygdala, int. capsule, thalamus (ant., lat., vent. n.), optic radiation, Sylvian gyrus	15
2900	Infarction putamen, globus pallidus, caudate n., amygdala, int. capsule, thalamus (ant., lat., vent. n.), optic radiation	12
2904	Infarction putamen, globus pallidus, caudate n., amygdala, int. capsule, hypothalamus (lat. n.), thalamus (ant., lat., vent., dorsomed. n.; pulvinar; lat. geniculate body), subthalamus, optic radiation	15
2908	Infarction putamen, globus pallidus, caudate n., amygdala, int. capsule, hypothalamus (lat. n.), thalamus (lat., vent., dorsomed. n.; pulvinar; lat. geniculate body), optic radiation, Sylvian, supra-Sylvian, ecto-Sylvian gyri	15
2971	Infarction putamen, globus pallidus, caudate n., amygdala, int. capsule, hypothalamus (lat. preoptic area, lat. n., fornix), thalamus (ant., lat., vent., dorsomed. n.)	10
2980	Infarction putamen, globus pallidus, caudate n., amygdala, int. capsule, hypothalamus (lat. preoptic area, lat. n., supraoptic n., fornix), thalamus (ant., lat., vent., dorsomed. n.), subthalamus	15
3034	Infarction putamen, globus pallidus, caudate n., amygdala, int. capsule, optic tract, hypothalamus (lat. and med. preoptic areas; lat., supraoptic, ventromed. n.; fornix), thalamus (ant., lat., vent., dorsomed. n.; pulvinar, lat. and med. geniculate bodies), Sylvian gyrus	15
3262	Infarction putamen, globus pallidus, amygdala, int. capsule, ectolateral gyrus	6
3420	Infarction putamen, globus pallidus, caudate n., amygdala, int. capsule, optic tract, hypothalamus (lat. n.), thalamus (ant., lat., vent., dorsomed. n.; lat. and med. geniculate bodies), subthalamus, optic radiation	15
3433	Infarction putamen, globus pallidus, caudate n., amygdala, int. capsule, optic tract, hypothalamus (lat. preoptic area; lat., supraoptic n.), thalamus (lat., vent., dorsomed. n.; lat. and med. geniculate bodies), subthalamus, optic radiation, Sylvian gyrus	15

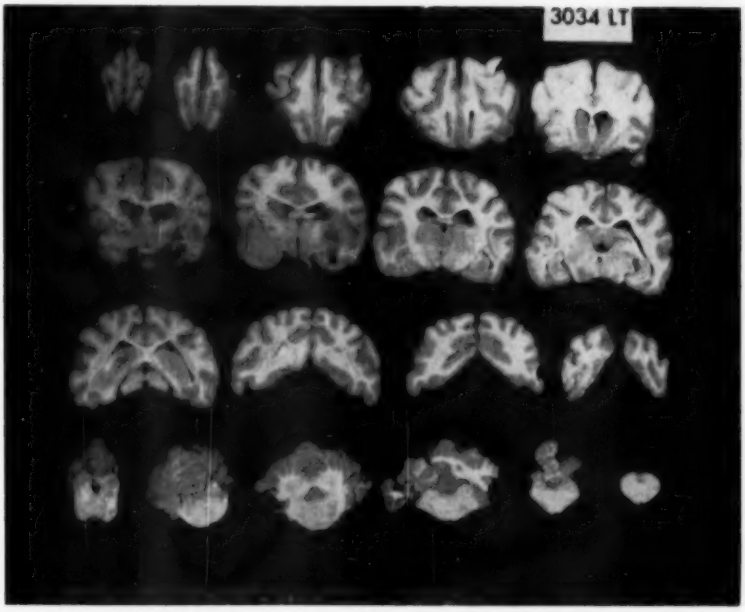

Fig. 2.—Coronal sections of a dog brain following interruption of the left middle cerebral artery at normal body temperature.

time of reaching a body temperature of 24 C were plotted simultaneously against the neurological score. The data indicate that maximum protection against infarction was obtained if hypothermia was initiated within 15 minutes of the vascular occlusion and if the 24 C level was reached within a total elapsed time of 90 minutes. If these times were exceeded, a secondary zone was found in which the results were unpredictable, ranging from maximum to minimum protection. The secondary zone for the delay time was 15-30 minutes and for the total elapsed time was 90-114 minutes. If these times were surpassed, no protection was found, and the animals developed infarcts which were as severe as those seen in the normothermic controls. There were three dogs in which more extensive disability would have been expected in view of the long delay times, 55 and 60 minutes, but in which only slight impairment was found.

Coronal sections of the brain of a dog that manifested no abnormal neurological signs are shown in Figure 4. This dog had a delay time of 30 minutes and a total elapsed time of 109 minutes. Only minor pathologic evidence of damage was found. This is consistent with previous experience in which it was demonstrated that the absence of clinical signs did not necessarily indicate the absence of infarction. Only 2 of the 15 dogs in Part I of this study, in which the middle cerebral artery had been interrupted during hypothermia, developed no infarct. The remainder had infarcts, but they were small and restricted to relatively "silent" areas. The lesion in Figure 4 would correspond to that found in the latter group.

Figure 5 is a composite of brain sections at approximately corresponding anatomical levels from six dogs in this study. The sections have been arranged in order of increasing disability, as determined from the calculation of the neurological score. Although, in this figure the extent of damage in *9* appears to be as great as that in *12* and *15*, microscopic study demonstrated that the area of infarction did increase in each suc-

TABLE 2.—*Segmental Resection of the Middle Cerebral Artery Followed by the Induction of Hypothermia*

Dog No.	Occlusion Temp., ° C.	Delay Time, Min.	Hypothermia Time, Min.	Total Elapsed Time, Min.	Low Temp., ° C.	Rewarming, Time, Min.	Results	Neurological Score
3191	36.0	0	81	81	21.1	90	Infarction putamen, globus pallidus, amygdala	0
3118	34.6	1	77	78	21.3	120	Infarction putamen, globus pallidus, amygdala, adj. int. capsule	0
3079	36.0	5	80	85	20.7	90	Infarction putamen, globus pallidus, amygdala, adj. int. capsule, Sylvian gyrus	0
3190	37.0	10	84	94	21.4	87	Infarction putamen, globus pallidus, amygdala, caudate n., adj. int. capsule, Sylvian gyrus	6
3499	35.0	15	78	93	22.9	98	Infarction putamen, globus pallidus, adj. int. capsule	1
3187	35.2	15	99	114	21.0	111	Infarction putamen, globus pallidus, amygdala, int. capsule, thalamus (lat. & med. geniculate bodies), optic radiation	7
3006	37.0	15	75	90	23.0	140	Infarction putamen, globus pallidus, amygdala, int. capsule, hypothalamus (ventromed., dorsomed. n., fornix), thalamus (lat. & med. geniculate bodies), optic radiation	8
3383	35.0	15	90	105	21.9	139	Infarction putamen, globus pallidus, amygdala, int. capsule, caudate n., subthalamus, thalamus (ant., vent., lat., dorsomed. n., lat. & med. geniculate bodies), optic radiation, Sylvian gyrus	14
3390	36.5	20	70	90	20.8	112	Infarction putamen, globus pallidus, amygdala, int. capsule, optic radiation	0
3346	36.5	20	75	95	22.3	90	Infarction putamen, globus pallidus, amygdala, caudate n., int. capsule, thalamus (ant., vent., dorsomed. n.; lat. & med. geniculate bodies), optic radiation	3
3196	34.7	20	59	79	21.0	109	Infarction putamen, globus pallidus, amygdala, int. capsule, lat. geniculate body, optic radiation	6
3320	36.2	20	82	102	21.3	105	Infarction putamen, globus pallidus, amygdala, int. capsule, thalamus (ant., vent. n.; lat. geniculate body), optic radiation	11
3474	35.5	25	67	92	22.2	86	Infarction putamen, globus pallidus, amygdala, caudate n., int. capsule, hypothalamus (lat., paraventricular n.; fornix), optic tract thalamus (ant., vent., lat., dorsomed. n.; lat. & med. geniculate bodies), optic radiation	4
3475	36.5	25	70	95	21.7	140	Infarction putamen, globus pallidus, amygdala, caudate n., int. capsule, thalamus (ant., vent., dorsomed. n.)	5
3501	37.0	25	74	99	21.8	81	Infarction putamen, globus pallidus, amygdala, caudate n., int. capsule, thalamus (ant., vent. n.; lat. & med. geniculate bodies; pulvinar), subthalamus, optic radiation	10
3269	36.7	25	85	110	21.0	84	Infarction putamen, globus pallidus, amygdala, caudate n., int. capsule, hypothalamus (lat. n.), thalamus (ant., vent. n.), optic tract	12
3103	36.0	30	79	109	21.2	103	Infarction putamen, globus pallidus, amygdala, adj. int. capsule, med. parasolfactory area, hypothalamus (lat. n.)	0
3197	35.2	30	67	97	22.5	114	Infarction putamen, globus pallidus, amygdala, caudate n., int. capsule, optic tract, thalamus (ant., vent., lat., dorsomed. n.)	9

3240	36.0	30	95	125	22.8	98	Infarction putamen, globus pallidus, amygdala, caudate n., int. capsule, med. parsolfactory area, thalamus (ant., lat., vent., dorsomed. n.), subthalamus, optic tract, ecto-Sylvian gyrus	13
3000	37.0	30	144	174	23.0	120	Infarction putamen, globus pallidus, amygdala, caudate n., int. capsule, hypothalamus (lat., supraoptic n.), thalamus (ant., lat., vent., dorsomed. n.; pulvinar; lat. & med. geniculate bodies), Sylvian gyrus	15
3053	36.6	55	94	149	22.5	136	Infarction putamen, globus pallidus, amygdala, int. capsule, med. parsolfactory area, thalamus (vent. n.), optic radiation, Sylvian supra-Sylvian ecto-Sylvian gyri	3
3401	38.0	55	58	113	21.8	113	Infarction putamen, globus pallidus, amygdala, int. capsule caudate n., thalamus (lat., vent. n.; pulvinar; lat. & med. geniculate bodies), optic radiation, Sylvian, ecto-Sylvian gyri	14
2950	35.0	60	104	164	22.5	85	Infarction putamen, globus pallidus, amygdala, int. capsule, med. parsolfactory area, thalamus (lat. & med. geniculate bodies), optic radiation	2
3931	36.6	60	75	135	22.5	112	Infarction putamen, globus pallidus, amygdala, int. capsule, med. parsolfactory area thalamus (ant. n.)	3
3037	37.0	60	85	145	22.5	137	Infarction putamen, globus pallidus, amygdala, caudate n., int. capsule, hypothalamus (lat., supraopt. n., fornix), thalamus (ant., lat., vent., dorsomed. n.; lat. & med. geniculate bodies pulvinar), subthalamus, optic tract	15
3318	37.5	105	100	205	21.8	112	Infarction putamen, globus pallidus, amygdala, caudate n., int. capsule, optic tract, thalamus (ant., lat. vent., dorsomed. n.; pulvinar; lat. & med. geniculate bodies), optic radiation	14
3987	37.5	120	129	249	22.8	108	Infarction putamen, globus pallidus, amygdala, caudate n., int. capsule, optic tract, thalamus (ant., lat., vent., dorsomed. n.; pulvinar; lat. & med. geniculate bodies), optic radiation	15
	Means	36.2		84.3	21.90	108.1		

cessive section. Such correlation was not precisely accurate in each instance, primarily because of the difficulty encountered in detecting minor neurological abnormalities, especially partial visual field deficits. However, in general, the severity of pathologic change was commensurate with the neurological score. Therefore, it was felt that the degree of correlation was good enough to allow the use of the neurological score as an index for comparing the experimental results.

Comment

The purpose of this investigation has been to study the effects of hypothermia upon the physiology of cerebral circulation, and, in particular, how these effects may be used to advantage in the treatment of cerebrovascular disease. In the first phase of this study it was demonstrated that the middle cerebral artery could be permanently interrupted without necessarily producing infarction, if the body temperature was reduced to 22-24 C at the time of the interruption. This finding had several important implications. 1. It provided additional evidence that end-arteries do not exist in the brain, not only confirming the anatomical demonstrations of vascular continuity,[2,7] but also indicating that, functionally, cerebral arteries do not act as end-vessels under the conditions imposed by hypothermia. 2. It suggested the possibility that the time interval from occlusion of a single major cerebral artery to the point where infarction occurs is longer than the periods observed following total cerebral circulatory arrest, 3 minutes 25 seconds [8] or 8 minutes.[9]

Indeed, this has been shown to be true by Harvey and Rasmussen, who demonstrated that 30 minutes of continuous occlusion of the middle cerebral artery was necessary before infarction occurred.[10] When occlusion was maintained longer than 30 minutes, infarction developed which increased in severity thereafter, until the elapsed time reached 50 minutes. At the 50-minute point, the degree of necrosis was as great as that

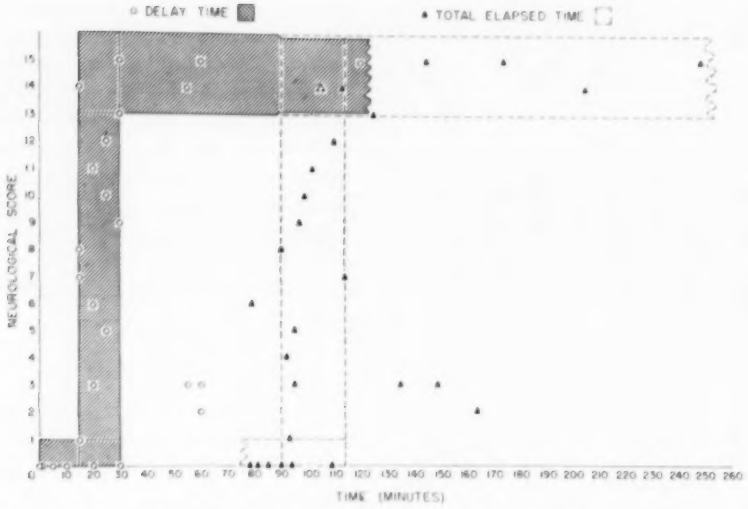

Fig. 3.—Effect of hypothermia following interruption of the middle cerebral artery upon the neurological score.

observed following permanent occlusion. Such a result was to be anticipated, since occlusion of a single artery like the middle cerebral does not result in cessation of flow distal to the interruption.[11-14] Instead, it can be postulated that a state of vascular insufficiency develops, wherein the presence of some circulation allows the partial replacement of the diminishing oxygen stores. However, supply cannot keep pace with de-

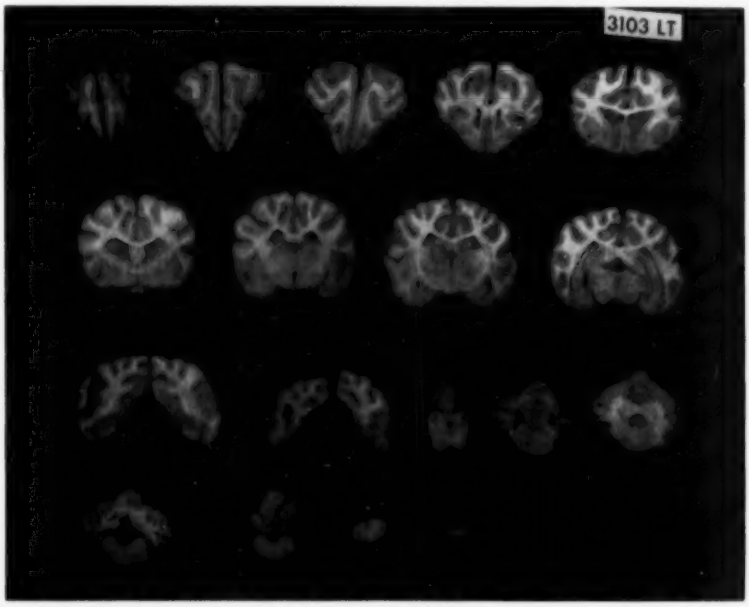

Fig. 4.—Coronal sections of a dog brain in which hypothermia was induced 30 minutes following interruption of the left middle cerebral artery.

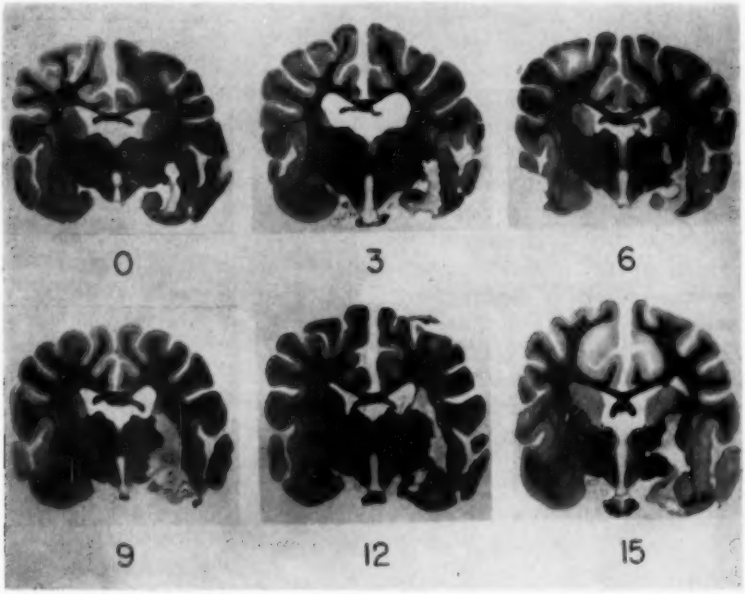

Fig. 5.—Comparison of the neurological score with the severity of pathologic change. Scores 0, 3, 6, 9, 12, 15; Dogs No. 3190, 2931, 3196, 3197, 2900, 3000, respectively.

mand, and eventually a critical point is reached where infarction occurs. The interval preceding this end-point is longer than that which is seen with total circulatory arrest, for with total arrest the oxygen supply cannot be even partially replenished. Therefore, that quantity present at the time of the arrest is exhausted in a much shorter period, and death of tissue ensues earlier.

The present experiments permitted some interesting observations of the type of blood flow that exists distal to an arterial occlusion. When the middle cerebral artery was occluded at its origin, an immediate strong pulsatile flow was found distal to the clip. When a second clip was placed just proximal to the first major cortical bifurcation, an isolated arterial segment was created whose only intact vascular connection was with the central striatal vessels. These vessels are said to have no anastomoses between the surface and the capillary bed, except for a few precapillary ramifications.[15] Yet, when this segment was opened, blood flow at a slow rate was still present, which appeared to be nonpulsatile in nature. This suggested that retrograde flow can occur not only through the meningeal anastomoses but through the capillary bed as well.

It was further deduced that the time interval for redistribution of blood flow from adjacent areas with intact blood supply into an area whose supply has been interrupted is probably in the range of 30 minutes to 3 hours. The lower limit was derived from the work of Harvey and Rasmussen; the upper limit was derived from the data of Part I of this study, in which collateral circulation was established within three hours, the total period of hypothermia. This, then, suggested a therapeutic approach to cerebrovascular disease, namely, that infarction may be averted if the vascular supply or metabolic demand in the area of distribution of an occluded artery were altered so as to reduce the disproportion between the two, i. e., increased supply or decrease demand or both.

The presently reported studies are an attempt to evaluate experimentally this type of therapeutic approach, utilizing hypothermia as the means of effecting the change

in supply-demand ratio. A cerebrovascular occlusion was simulated by resecting the middle cerebral artery from its origin to the first major cortical bifurcation. This procedure was selected in preference to simple occlusion at the origin, since past experience had shown that resection, at normal body temperature, produces more consistent, extensive infarcts in the distribution of the artery.[1] Therefore, this provides the most rigorous experimental test of the hypothesis, probably one that is even greater than that created by the naturally occurring form of cerebrovascular occlusion. This statement is predicted by two facts: 1. Since the artery is permanently transected, there can be no opportunity for reestablishment of blood flow through the occluded vessel by relief of spasm, recanalization, etc. 2. An additional burden is imposed by the removal of the meningeal anastomoses of the artery by resecting the segment through which these ramifications communicate. This removes an important source of collateral blood flow,[16] leaving only precapillary and capillary anastomoses for the development of collateral circulation.

The results indicate that the use of hypothermia did effectively avert the consequences of arterial interruption if temperature reduction was initiated within 15 minutes of the occlusion and if a level of 24 C was reached within 90 minutes. This is evidence that the time interval from occlusion of a single major cerebral artery to the point where infarction occurs is longer than the 3- to 8-minute period cited for total circulatory arrest. Harvey and Rasmussen indicated that the interval was 30 to 50 minutes. The data from these experiments do not allow the calculation of this time, but they suggest an interval of the same order.

If certain assumptions are allowed, the theoretical time for the establishment of collateral circulation at normal body temperature may be estimated from the data of these experiments. These assumptions are as follows: First, cerebral tissue will respire at its full rate at normal body temperature even in the face of a low oxygen tension. The work of Elliot and Henry, who showed that brain tissue did respire at its full rate in the presence of oxygen tensions as low as 4 mm. Hg, suggests that this assumption is a valid one.[17] Second, cerebral oxygen consumption must decrease as a linear function of temperature, and temperature must decrease as a linear function of time during hypothermia. The experiments of Rosomoff and Holaday indicated that cerebral oxygen consumption was a linear function of temperature in the range investigated,[18] and a review of their unpublished data also revealed that oxygen consumption was a linear function of time when using a method of cooling which was identical with that used in the present study. Thus, the second assumption would appear to be valid. Third, the development of collateral circulation is a linear function of time. There is no evidence available to establish or negate this point. However, for purposes of this discussion, it is asked that this assumption be accepted with the full realization that a linear function may not exist. This is done in an attempt to estimate the order of magnitude of the time parameters involved in this problem, albeit this estimate may not be

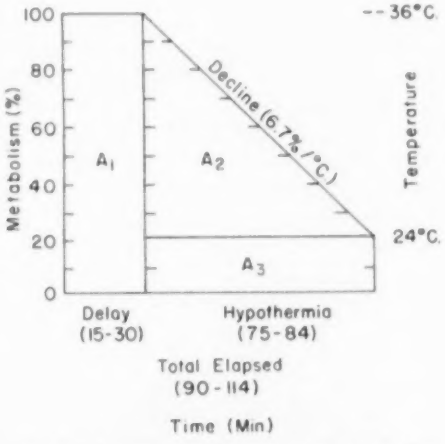

Fig. 6.—Schema for the estimation of the theoretical time for establishment of collateral circulation at a constant temperature of 36 C.

entirely accurate. Accepting these premises, the schema shown in Figure 6 may be drawn and the Areas A_1, A_2, and A_3 may be calculated. The sum of the areas is then divided by 100%, the assumed rate of metabolism at normal body temperature. The result is the theoretical time it would take at a constant temperature of 36 C for collateral circulation to become established, the term collateral circulation referring to the rerouting of blood through preexistent anatomical pathways, i. e., capillary, precapillary, and meningeal anastomoses. Substitution of the appropriate figures yields an estimated time range of 64 to 80 minutes. This calculation is submitted with the following qualification: As presented, the argument depicts simple relationships among the rate of metabolism, the rate of establishment of collateral circulation, and time. However, there is the possibility that hypothermia renders the cell less susceptible and/or dampens the response to injury, thereby producing an additional protective effect. Therefore, the derived figures may be an overestimate of the actual time for establishment of collateral circulation by an amount attributable to a possible intrinsic protective effect of hypothermia.

The feasibility of the use of hypothermia in the treatment of experienced cerebrovascular occlusions was demonstrated by this investigation. However, the question of the transposition of the experimental data to man is a moot point, as it is in all animal investigations, and can only be answered by trial. At first hand, the practicability of this technique would seem small, since it could be argued that it would be almost impossible to initiate hypothermia within 15 minutes of the ocurrence of a cerebrovascular accident in man, due to the time consumed in making the diagnosis and removing the patient to suitable facilities for the procedure. Yet, if one considers the prodromal signs which some patients manifest, sometimes well in advance of the onset of classical signs of infarction, and if one is alert to the possibilities offered by the use of hypothermia, the idea may not be as impractical as first thought.

However, there is one immediately apparent application of this technique. A considerable hazard in the surgery of cerebrovascular anomalies is the risk of accidental or intentional interruption of a major vascular channel. Therefore, it is suggested that hypothermia be used regularly as an adjunct in the neurosurgical treatment of these lesions. There are several advantages to be gained by the use of hypothermia, in addition to protection against the consequences of hypoxia. Among these are a decrease in cerebral blood flow, which facilitates hemostasis,[18] and a reduction in brain volume and intracranial pressure, which enhances surgical exposure.[19] In the limited clinical experience with hypothermia to date, most groups have been satisfied to stop the cooling process at 28 C, because of the increased incidence of extracerebral complications, i. e., cardiac arrhythmias, which occur below this temperature.[20-23] However, Lundberg has shown the practicability of deep hypothermia, 25 C, which his group has been able to utilize without incident and which approaches the range studied in this investigation.[24] This notwithstanding, the data suggest that when operating at 28 C, or even normal body temperature, if it should become necessary to ligate a major artery through intent or accident, there would still be sufficient time to resume or initiate cooling in order to reach the temperature levels at which protection against infarction may be obtained.

Summary and Conclusions

An acute cerebrovascular occlusion was simulated by resecting the left middle cerebral artery of the dog from its origin to the first major cortical bifurcation. Hypothermia was then induced after delays of from 0 to 120 minutes following initial occlusion of the artery. The animal was kept at a body temperature of 24 C or less for one hour, and then the dog was rewarmed to normothermic levels. It was demonstrated

that protection against infarction was obtained if hypothermia was initiated within 15 minutes of the occlusion and if a temperature of 24 C was reached within a total elapsed time of 90 minutes. It was concluded, therefore, that the use of hypothermia following interruption of the middle cerebral artery did protect against cerebral infarction in the dog.

J. Ewell, HM 3, U. S. N., and C. Pollnow, HN, U. S. N. R., assisted during the course of these experiments. Mrs. A. B. Snodgress and her staff prepared the histological material from this study, and M. H. Rhodes, HMC, U. S. N., and his staff gave photographic support.

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Psychomotility and Parkinsonism in Treatment with Neuroleptic Drugs

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Extensive clinical observations have left little doubt that the use of chlorpromazine and reserpine in psychiatry is most effective in the treatment of disorders which manifest themselves through a behavioral common path of hypermotility, hypernormal initiative, and increased affective tension. Although they differ greatly in chemical properties and neurophysiological action, both drugs inhibit psychomotor activity, frequently to the degree of extrapyramidal symptoms which share a variety of clinical features with the Parkinsonian syndrome. The pronounced effect of these drugs on mental syndromes which have their functional origin in subcortical regions induced Delay and Deniker [1] to propose the name "neuroleptics," a term which found the approval of the participants at the International Symposium on Chlorpromazine and Neuroleptic Drugs, held in Paris in October, 1955.

One is tempted to see more than a historical coincidence in the fact that these neuroleptic drugs came our way at a time of fundamental changes in concepts of brain function. Hess [2] demonstrated the functional integration of the diencephalon with the extrapyramidal motor system and refers to "diencephalic motor innervation." His work convinced him that the diencephalon, rather than the cortex, is to be regarded "as the true control organ of the body." Penfield and Jasper [3] postulate the existence of a "centrencephalic system" as the highest level of functional integration. Magoun's mesencephalic and diencephalic activating systems strongly support the assumption of subcortical functional primacy.

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The earliest clinical trials with chlorpromazine, in France, and with reserpine, in Switzerland, provided evidence that the therapeutic effectiveness depended on the right choice of clinical symptoms, i. e., dysfunctions, rather than on nosologic entities. This has been the case with other somatic therapies which modify particular behavior disturbances, such as, for example, the elimination of depression of various clinical types through electroconvulsive therapy. The emergence of hypermotility and related psychokinetic disturbances as criteria for neuroleptic therapies necessitated a differentiation of clinical diagnoses in relation to psychomotor behavior. The problem of therapeutic evaluations, thus, becomes substantially one of double bookkeeping: a descriptive elaboration of particular modes of behavior and the recording of the associated clinical diagnoses. Little information can be gained from clinical statistics, which, for example, report success or failure with neuroleptic drugs in the treatment of "depressive psychoses" without distinguishing between depressions characterized by psychomotor retardation and apathy and those with manifestations of restlessness and agitation. Yet it can hardly be surprising that drugs which inhibit psychomotor activity are therapeutically ineffective in those psychopathological states which manifest themselves through depressive constriction, affective lameness, and decreased initiative in the first place. On the contrary, therapeutic benefits are most frequently, and often dramatically, apparent in psychopathological states which are associated with hypernormal drive, uncontrolled impulsivity, and emotional excitement, since the in-

hibitory action on psychomotility restores a psychokinetic equilibrium and, thus, contributes to the harmonization of the personality. One is able, it appears, to influence complex cerebral mechanisms which determine and alter psychomotor expression. The resulting reduction of psychokinetic activity is of a decrescendo nature, ranging from ordinary lassitude and passiveness to extreme Parkinsonian rigidity. Initially, many observers looked upon this extrapyramidal syndrome as a complication unrelated to the normal action of the drugs and assumed a toxic reaction. Our first observations,[4] in 1954, suggested to us, and our subsequent studies strengthened the impression, that we were dealing with a regular effect of neuroleptic drugs, part and parcel of their therapeutic action, which in many instances makes it seem arbitrary to define borderlines between therapeutic quanta of hypomotility and early signs of Parkinsonism.

Haase[5] described typical changes in the handwriting (rigidity, micrographia) of 86% of his patients receiving chlorpromazine, whereas only a fraction showed the grosser symptoms of a Parkinsonian syndrome. He sees in the psychomotoric Parkinsonian syndrome the *conditio sine qua non* of the desired effect in psychiatric therapy. Ditfurth[6] noted that cogwheel rigidity of the shoulder muscles preceded other signs of Parkinsonism. He, too, interpreted striopallidal symptoms as regular effects of chlorpromazine therapy. Haase, and Delay and Deniker also commented on significant differences of the Parkinsonian syndrome observed during reserpine therapy. Here a picture of increasing motor restlessness occurs frequently which resembles the phenomena of *kinesia paradoxa* and *akathisia*, described as variations of paralysis agitans by Bing.[7] Walther-Büel[8] wondered whether neuroleptic drugs could contribute to a pharmacological analysis of extrapyramidal disturbances, since they are, in a sense, antagonists to the anti-Parkinsonian agents. The neurological polarity between Parkinsonism and chorea induced him to use chlorpromazine and reserpine in the treatment of Huntington's chorea. He reported favorable results, as did Lazarte.[9]

Neuroleptic drugs confront one with an unusual variety of individual differences in responsivity. In a previous report[10] we analyzed some of the factors which contribute to the high variability of reactions, since our data did not support the assumption of a correlation of side-reactions and complications with duration of treatment or drug quantity. While it is true, for example, that small doses of chlorpromazine (25-75 mg. daily) or of reserpine (1-3 mg. daily) are least likely to produce undesirable effects, they fall also far below the range of therapeutic potency in psychiatric disorders.

The following report concerns incidence and clinical manifestations of Parkinsonism in a series of patients treated with either chlorpromazine or reserpine between March, 1954, and February, 1956.

Material and Method

All patients were hospitalized. They were new or recent admissions or were chronic patients who had remained intensively psychotic in spite of other therapies. At no time did we combine drug therapy with other somatic procedures (ECT, insulin shock, or use of sedatives). The main purpose of this investigation was the assessment of neuroleptic therapies on their own merits. The majority of acutely disturbed or restless patients received chlorpromazine medication i. m. for five to eight days before an abrupt or a gradual substitution of oral medication took place. Reserpine was given by injection for longer periods before a shift to oral medication seemed practical. Separate daily charts were kept by doctors and nurses to record clinical and behavioral changes, with special emphasis on the psychomotor aspects before, during, and at termination of therapy. Table 1 illustrates the diagnostic composition of the total number of patients in each series.

Observations

Table 2 reveals the incidence of Parkinsonism in relation to clinical diagnoses. Parkinsonism developed in 58 patients, or 10.7% of all patients treated with chlor-

TABLE 1.—*Clinical Diagnosis*

Diagnosis	No. of Patients	
	Chlorpromazine	Reserpine
Schizophrenia	274	54
Manic psychoses	38	10
Other affective psychoses	57	9
Psychoneuroses	25	5
Organic syndromes	94	27
Drug or alcohol addiction	38	4
Personality disturbances	15	3
Total	541	112

promazine, and in 19 patients, or 16.9% of those treated with reserpine.

It must be said from the outset that this selection of patients with Parkinsonism is merely an approximation, and a rather conservative one at that. The gradual reduction of psychokinetic activity cannot be compartmentalized into normal versus extrapyramidal modes of motility patterns. A measure of poverty of movement and facial fixity can be observed in the greater majority of all patients during therapy. Very fine tremors can easily be overlooked. The similarity of motor disturbances in schizophrenia—for example, muscular rigidity, negativism, and stereotypical movements of catatonic or hebephrenic patients—can obscure the early and mild manifestations of extrapyramidal symptoms, such as the loss of associated movements. Similarly to the Parkinsonian syndrome which appears in a rudimentary form in the normal motility of old age, Parkinsonism as encountered with chlorpromazine and reserpine sometimes develops in a slow fashion, varying greatly in degrees of intensity. Not infrequently, however, one witnesses a radical transformation from superabundance to a restricted economy of movement, which temporarily changes the temperamental characteristics of the patient and makes him accessible to psychological and social approaches.

TABLE 2.—*Diagnoses of Patients with Parkinsonism*

Diagnosis	Chlorpromazine	Reserpine
Schizophrenia	35	13
Manic psychoses	4	1
Other affective psychoses	5	3
Psychoneuroses	3	
Organic syndromes with		
(*a*) Alcoholism	2	—
(*b*) Senility	3	—
(*c*) Cerebral arteriosclerosis	2	2
(*d*) CNS syphilis	1	—
(*e*) Mental deficiency	2	—
Organic syndromes of unknown cause	1	—
Total	58	19

Patients reported as having shown Parkinsonism manifested tremors, cogwheel phenomena, facial rigidity (wooden expression), and gait disturbances. These symptoms occurred in various combinations, ranging from moderate to severe degrees of intensity. Drooling is rare with chlorpromazine but frequent with reserpine.

The manifestations were sufficiently severe in 26 patients with chlorpromazine Parkinsonism (4.8% of all patients) and in 8 with reserpine Parkinsonism (7.1% of all patients) to necessitate termination of treatment. Early in our investigation we stopped medication more easily than later, when we were better acquainted with the action of the drugs. In some instances, on lowing difficulties became alarmingly severe. the other hand, rigidity, drooling, and swal- Two chlorpromazine patients developed board-like rigidity of the abdominal wall, associated with marked distention due to hypomotility of the intestine. Discontinuation of medication brought rapid relaxation of the abdominal muscles and saved the patients from surgical exploration of what had appeared to be "acute surgical abdomen."

Reserpine Parkinsonism is more apt to be severe and varies insofar as motor restlessness occurs more frequently. Patients complain of "inner unrest" and have at times an irresistible urge to be in motion. They pace the halls, sleep poorly at night, and prefer to be up and around. Such motor patterns seem to be identical with akathisia as known from cases of paralysis agitans. Moreover, they are reminiscent of the hyperkinetic behavior of encephalitic patients, especially the children in the postencephalitic phases. Table 2 does not include patients with these reactions. Clinical evaluations provide, nevertheless, convincing evidence that these phenomena belong in the

province of Parkinsonism. It can be estimated that the addition of patients showing these symptoms would increase the incidence of reserpine Parkinsonism by 6%-8%.

One patient with a chronic postencephalitic brain syndrome died during treatment with reserpine. He is not included in the material of this study, since he had Parkinsonism to begin with. There had been reports in the literature[11] that tremors associated with true Parkinson's disease subsided in response to chlorpromazine and reserpine. This patient was admitted to the Delaware State Hospital in 1949. He showed a typical chronic encephalitic brain syndrome, with marked tremors, rigidity, and gait disturbances. Various anti-Parkinsonian drugs were administered through the years but were only moderately effective. A trial with chlorpromazine had to be abandoned after six days (100 mg. daily) because tremors and rigidity increased. Six months later reserpine was given (5 mg. i. m.; 2 mg. p. o. daily). Within two days he became totally rigid, could neither sit nor walk, and had to be lifted. On the third day he had the appearance of a wooden figure. He died suddenly that night, apparently of respiratory arrest while asleep. In two other cases with paralysis agitans, chlorpromazine aggravated the tremors. The fact that neuroleptic drugs not only produce an extrapyramidal syndrome of a Parkinsonian-like nature but enhance the symptoms of true striopallidal disease strongly suggests a common site of action.

Table 3 shows the dates of onset of chlorpromazine Parkinsonism within 10-day periods. These data suggest that individual susceptibility rather than duration of medication plays a decisive role, since more than 50% of the patients developed the symptoms before the 20th day.

TABLE 3.—*Time of Onset (Chlorpromazine)*

No. of Days	No. of Cases Having Developed Parkinsonism	Percentage	Percentage by Accumulation	
			%	Days
1- 10	6	10.3	10.3	up to 10
11- 20	25	43.1	53.4	up to 20
21- 30	4	6.9	60.3	up to 30
31- 40	9	15.5	75.8	up to 40
41- 50	0		75.8	up to 50
51- 60	3	5.2	81.0	up to 60
61- 70	4	6.9	87.9	up to 70
71- 80			87.9	up to 80
81- 90	4	6.9	94.8	up to 90
90-100	1	1.7	96.5	up to 100
More than 100	2	3.5	100.0	more than 100 days

TABLE 4.—*Time of Onset (Reserpine)*

No. of Days	No. of Cases Having Developed Parkinsonism	Percentage	Percentage by Accumulation	
			%	Days
1- 10	2	10.5	10.5	up to 10
11- 20	5	26.3	36.8	up to 20
21- 30	7	36.8	73.6	up to 30
31- 40	2	10.5	84.1	up to 40
41- 50	0		84.1	up to 50
51- 60	1	5.3	89.4	up to 60
61- 70	0		89.4	up to 70
71- 80	0		89.4	up to 80
81- 90	0		89.4	up to 90
90-100	1	5.3	94.7	up to 100
More than 100	1	5.3	100.0	more than 100 days

A very similar pattern of chronological development characterizes reserpine Parkinsonism, as illustrated in Table 4.

No correlation of Parkinsonism and dosage seems to exist, as demonstrated in Tables 5 and 6.

Onset of Parkinsonism is shown in relation to total dosage when symptoms became apparent. Although these collective tabulations do not provide information on patterns of individual daily doses, they reveal rather impressively the absence of any apparent dependence of Parkinsonism on total amounts of medication which patients had received when they manifested evidence of Parkinsonism. It seems to be less plausible to attribute a causative role to toxicity than to assume that one is dealing with factors associated with certain individuality differentials.

Tables 7 and 8 demonstrate that Parkinsonism from drugs is totally unrelated to particular age levels, occurs in the very young as well as in the very old, and can,

TABLE 5.—*Total Dosage at Onset (Chlorpromazine)*

Dosage, Mg.	No. of Cases	Percentage
0-10,000	25	43.1
10,000-20,000	21	36.2
20,000-30,000	6	10.3
30,000-40,000	1	1.7
40,000-50,000	2	3.5
50,000 and more	3	5.2
Total	58	100.0

TABLE 6.—*Total Dosage at Onset (Reserpine)*

Dosage, Mg.	No. of Cases	Percentage
0-100	2	10.5
100-200	10	52.7
200-300	2	10.5
300-400	3	15.8
400-500		
More than 500	2	10.5
Total	19	100.0

thus, not be connected with aging processes which favor the development of paralysis agitans.

The most perplexing aspect of drug-induced Parkinsonism concerns the sexual differences. Tables 9 and 10 seem to provide evidence of a constitutional differential of high specificity. More than twice the number of patients with chlorpromazine Parkinsonism were female, as were almost twice the number of patients with reserpine Parkinsonism.

TABLE 7.—*Relation of Age to Chlorpromazine Parkinsonism*

Age Group, Yr.	All Patients	Patients with Parkinsonism	% of Total Age Group
0-19	12	4	33.3
20-29	64	9	14.1
30-39	132	10	7.6
40-49	121	10	8.3
50-59	98	13	13.3
60-69	55	7	12.7
70-79	48	3	6.3
More than 80	11	2	18.2
Total	541	58	10.7

A chance phenomenon can be regarded as unlikely, since the differential ratio appeared early in this study and has prevailed since. Furthermore, no other variable in the series shows any degree of correlation with sex. Interestingly enough, therapeutic evaluations failed to reveal differences of the final results in relation to sex. The assumption of some authors that a favorable psychiatric response depends on the development of Parkinsonism during treatment is, therefore, shown to be doubtful.

TABLE 8.—*Relation of Age to Reserpine Parkinsonism*

Age Group, Yr.	All Patients	Patients with Parkinsonism	% of Total Age Group
0-19	1	None	0.0
20-29	4	2	50.0
30-39	21	3	14.3
40-49	28	5	17.9
50-59	23	5	21.7
60-69	20	3	15.0
70-79	11	1	9.1
More than 80	4	None	0.0
Total	112	19	17.0

TABLE 9.—*Sexual Differences of Parkinsonism (Chlorpromazine)*

	Total No. of Patients	Patients with Parkinsonism	
		No.	% of Total
Males	236 (43.6%)	15	6.4
Females	305 (56.4%)	43	14.1
	541	58	

An influence of chlorpromazine on hormonal actions has long been apparent. Lactation in nonpregnant women is not uncommon. Menstrual irregularities during and after treatment courses are frequent. Some psychotic women begin to menstruate after years of amenorrhea. Changes in metabolism have been postulated as causes of vegetative stabilization and weight increase which frequently accompany favorable therapeutic responses. Some investigators reported evidence of a peripheral cellular action of chlorpromazine, while others refer to a pituitary-hypothalamic mechanism. A specific property of chlorpromazine, however, remains questionable, since reserpine produces similar effects on the striopallidal system in spite of its different chemical composition and pharmacological action. The available literature does not mention sexual differences in the incidence of Parkinsonism. Our observations need further substantiation. Yet there is little doubt that the sex factor appears to be of major importance. One must wonder why women show this higher frequency of drug-induced extrapyramidal syndromes, whereas men bear the brunt of idiopathic Parkinson's disease.

TABLE 10.—*Sexual Differences of Parkinsonism (Reserpine)*

	Total No. of Patients	Patients with Parkinsonism	
		No.	% of Total
Males	56 (50%)	7	12.5
Females	56 (50%)	12	21.4
	112	19	

Comment

The already momentous literature on chlorpromazine and reserpine offers surprisingly little information on occurrence and significance of Parkinsonism. Most reports refer to Parkinsonism as a toxic side-effect or neurotoxic reaction.[12] Many blame dosage or duration of treatment without the supportive evidence of clinical statistics. May and Voegele,[13] reporting four cases of Parkinsonian reactions (all women, incidentally), commented that "the drug-induced Parkinsonian reaction seems to be physiologic and always reversible and to be a function of total dosage rather than a toxic symptom." A precise definition of toxicity is always a controversial matter, since one can designate any undesirable symptom as toxic. A difference exists, nevertheless, between manifestations which constitute an excessive degree of a desired effect reflecting the regular action of a given drug and reactions involving organs or organ systems not related to the site of the drug's regular action. On the basis of this distinction, Parkinsonism cannot be regarded as a toxic reaction.

A meaningful interpretation of Parkinsonism presents itself in connection with psychomotility and its modification by the neuroleptic drugs. The sphere of psychomotility has been conceptualized as including volitional, impulsive, and effective functions. The regulation of these functions depends on the coordination of extrapyramidal, diencephalic, and mesencephalic systems, as elaborated by Hess, Penfield, and others. This integration signifies the therapeutic potentialities of drugs which affect the functions of these subcortical systems. What we observe as the psychiatrically most favorable therapeutic effect can be defined as a process of harmonization of the personality, characterized by vegetative stabilization, as well as by attenuation of impulsivity, excessive drive, and motor activity. Since consciousness and ideation remain intact, it seems proper to speak of a selective effect on the kinetic components of psychopathological states. Therapeutic application must, therefore, be based on knowledge of psychokinetic elements in the patient's temperamental disposition and psychopathological behavior. Compulsively active patients often experience overwhelming anxiety in reaction to the drug-induced loss of initiative, since it is essential for them to neutralize anxiety through physical activity. The experiential aspects, i. e., the manner in which patients experience the drug's effects, must be carefully analyzed if therapeutic failures are to be avoided. Thus, a growing number of patients are found to develop depressions during reserpine therapy prescribed for hypertension, nervousness, and "functional" disorders. Far from being psychogenic, these depressions are pharmacological in origin and suggest for the greater part errors of therapeutic judgment concerning the temperamental and symptomatic aspects of the patient. Unfortunately, the concept of "tranquilization" possesses dangerous implications. It lacks any measure of therapeutic specificity and conveys the seductive promise of peace of mind for everybody. One cannot stress sufficiently that "tranquility" means many things to many people, hardly to be produced by identical chemical means.

Clinical experience points the way toward fuller recognition of the specific potentialities of neuroleptic drugs. The frequency of Parkinsonism and the varieties of its manifestations strongly support the assumption of a regular effect on the striopallidal system. We, therefore, need to reevaluate the role of psychokinetic factors in psychopathology in order to assess the therapeutic advantages of their modification. One can observe that some of the most excited and agitated patients react with the severest degree of Parkinsonism. Such a shift from extreme hyper- to extreme hypomotility stimulates questions pertaining to the striopallidal system and its involvement in psychotic syndromes. One of the most disturbed female patients, showing episodic

catatonic excitement for many years, developed pronounced Parkinsonism during three separate courses, two with chlorpromazine and one with reserpine. Instead of being uncontrollably agitated, destructive, and assaultive, this patient underwent in each of three courses a transfiguration into robot-like rigidity, with swallowing difficulties and tremors. Three other female patients developed Parkinsonism for the second time when a repeat course of chlorpromazine was initiated, while another female patient had three courses of chlorpromazine, each single time with pronounced Parkinsonism. One male patient with two courses of reserpine manifested Parkinsonism in both.

While a special study of patients with multiple courses of neuroleptic drugs is now in progress, these observations indicate already that Parkinsonism recurs in certain patients during each course of therapy with both chlorpromazine and reserpine, given singly or interchangeably. Such recurrence devaluates still further the assumption of a toxic reaction, since it eliminates desensitization, which plays a significant part in jaundice [14] and skin reactions. Moreover, anti-Parkinsonian drugs, of which procyclidine hydrochloride proves to be especially effective in our experience, ameliorate tremors and rigidity very successfully. We are, therefore, justified in postulating a polarity of pharmacological action between the neuroleptic and the anti-Parkinsonian agents.

There remains the question of the nature of individual susceptibility, without which it would be difficult to explain the range of variation in extrapyramidal manifestations. The prominent role of the sex differential has already been mentioned. Other dispositional factors may be involved which cannot yet be clearly identified. In a rather substantial number of cases, we found multiple evidence of familial mental and nervous diseases. In at least two, and probably three, instances the patient had a parent suffering from paralysis agitans. Several patients had previously suffered from traumatic, toxic, or infectious encephalopathies. Individual psychomotor patterns in the sense of a constitutional "extrapyramidal endowment," as assumed by Kretschmer [15] and others, may exert a predisposing influence. It is certainly conceivable that there exist individual differences in the manner in which cortical and subcortical motor systems are functionally integrated. The qualitative and quantitative representation of component systems would then account for the continuum of normal to abnormal psychomotor patterns. Such elements of individuality must be given consideration in the experimental search for neurophysiological causes of drug Parkinsonism.

In a speculative sense, it can be said that neuroleptic drugs, through their regular action upon the subcortical motor system, enhance predispositional or latent factors which facilitate Parkinsonism. Whatever the true connections may turn out to be, the fact that we now possess drugs which alter the functional balance of the extrapyramidal system and can produce a reversible Parkinsonian syndrome opens up new territories for research on interrelations of brain functions, psychomotor behavior, and psychopathology.

Summary

Chlorpromazine and reserpine are most effective in the treatment of those psychiatric disorders which have in common hypermotility, hypernormal initiative, and increased affective tension. Both drugs inhibit psychomotor activity in a manner which involves changes in the functional balance of the extrapyramidal motor system. If pronounced, these changes are associated with a clinical picture of Parkinsonism.

A two-year study of 653 psychiatric patients under treatment with chlorpromazine and reserpine revealed the incidence of Parkinsonism to be 10.7% and 16.9%, respectively. Neither diagnosis, age, duration of treatment, nor total dosage shows corre-

lation with Parkinsonism. These data do not support the assumption of toxicity as a causative factor.

A most significant sexual difference is apparent, since the frequency of Parkinsonism is twice as high in women regardless of the choice of drug. No explanation can be offered at present. This observation, however, together with other reported findings, suggests that individuality differentials account for the considerable range of physiological and psychological responses.

The property of neuroleptic drugs to produce Parkinsonism offers unique opportunities for investigations of psychomotor function and psychopathology.

Mr. William E. Kirsch, research associate, Smith, Kline & French Laboratories, Philadelphia, gave generous supplies of chlorpromazine. Part of the reserpine was contributed by the Ciba Pharmaceutical Products, Inc., Summit, N. J. Part of the procyclidine hydrochloride was contributed by the Burroughs Wellcome & Company, Inc., Tuckahoe, N. Y.

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Treatment of Myotonia with Procainamide

D. STUART MacROBBIE, M.D., and WALTER J. FRIEDLANDER, M.D., San Francisco

Disappointment in the use of a number of different therapies in the treatment of myotonia has led to the continuing search for more efficacious drugs. Geschwind and Simpson[1] in 1955 reported that procainamide was useful in the treatment of myotonia. The present report attempts to evaluate this drug further.

Method

There were seven patients in this clinical trial, six of whom had myotonia dystrophica and one who had myotonia congenita. All had definite myotonic reactions following voluntary contraction of the hand ("voluntary contraction myotonia"). In addition to a neurological work-up, pertinent endocrine and EKG studies were obtained. After a base line of behavior and activity was recorded, the patient was usually started on 2.0 mg. of procainamide hydrochloride U. S. P. daily by mouth in four divided doses, and then this was gradually increased by 0.5 to 1.0 gm. increments until the effective maintenance dose was reached. The patients were observed daily in the hospital for at least several weeks and then followed as outpatients. The opinions of the nursing staff, other patients, and at least three physicians were recorded. No placebo controls or ergographic studies were carried out. Electromyographic evaluation and motion pictures were taken of several patients before and after the drug was given. Frequent blood counts were obtained.

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Results

In all patients, oral procainamide produced significant diminution of the "voluntary contraction myotonia" except in one (Patient 6), in whom there was only a minimal degree of myotonia to start with; this was the single case of myotonia congenita. The results are summarized in the accompanying Table. However, even though the "voluntary contraction myotonia" was virtually abolished, the myotonia following percussion ("percussion myotonia") was not appreciably altered. Of the seven patients, the five with well-advanced myotonia dystrophica were aided enough to warrant definitely continuation of this not inexpensive drug. Improvement started within one hour after the oral administration of a single dose and continued noticeably for about four hours. Some patients claimed additional benefits, such as relief from chronic muscle stiffness and aching and

Results of Procainamide Hydrochloride Therapy in Myotonia

Patient	Age, Yr.	Daily Maintenance Dose, Gm.	Duration of Symptoms, Yr.	Degree of Dystrophy*	"Voluntary Contraction Myotonia"*	
					Before Drug	With Drug
1	36	4	20	+++	+++	+
2	41	4	16	++++	++++	++
3	28	4	10	++	++	+
4	39	4	13	+++	+++	+
5	50	3	13	+++	+++	+
6	30	4	7	−	+	+
7	44	3	3	+++	+++	+

* Minus sign (−) means none; +, minimal; ++, moderate; ++++, marked

increase of strength, stamina, and alertness. Several patients with thick speech and dysphagia suggested that these functions were better, but it was difficult to evaluate any of these changes objectively. Follow-up visits of 1 to 12 months has revealed no significant changes in the effectiveness of the drug, though the feeling of well-being has not continued to the same degree as when the patient first received the drug.

Although some of these patients had experienced toxicity from quinine in relative therapeutic dosage, none experienced side-effects with procainamide which were so unfavorable that the drug had to be discontinued. Side-effects were usually prevented by a gradual increase in the maintenance dose, or, if they did occur, they were eliminated by slight reduction of dosage. Epigastric distress and nausea were the commonest symptoms; these either were transient or disappeared when the dose was accompanied by a meal. Two patients complained of "heart pounding" and "faint feelings" a short time after each dose, but this disappeared in time. Two other patients complained of irritability and insomnia—one with violent dreams—but, again, reduction of the maintenance dose alleviated these difficulties.

A case representative of very good results was that of Patient 4, a 38-year-old white man who was known to have had myotonia dystrophica for 13 years. There had been slowly progressive weakness and wasting of the muscles of the upper and lower extremities, as well as of the sternocleiodomastoid muscles. His condition had been such that he had been unemployed for 10 years. He had complained of aching and stiffness of his muscles for years and had not found any relief for this. Examination revealed a balding, flabby, pallid man, with a drawn, expressionless face. His speech was thick. The sternocleiodomastoid muscles and distal portions of the limbs were wasted. He had a steppage gait. Percussion of the thenar eminences or voluntary contractions produced a marked myotonic response. Although tried previously on quinine, testosterone, thyroid, and pyrotherapy, he had not obtained any appreciable benefit; however, he did respond very favorably to procainamide hydrochloride. He was started on 0.25 gm. four times daily; the dosage was gradually increased to 4 gm. a day. The patient and those around him noticed that he was more alert and spontaneous in his behavior. His "voluntary contraction myotonia" was reduced almost beyond the point of detection, although his "percussion myotonia" remained about the same. He felt that he was stronger in his legs and showed it by a much greater steadiness, as well as stamina, in his walking. His diffuse aches and feelings of stiffness were greatly alleviated. Concomitantly, he started to socialize more on the ward and confided that he had not known the extent of his disability until he had obtained some relief from it.

Comment

Our results agree with those reported by Geschwind and Simpson in that most of our patients manifested diminution of "voluntary contraction myotonia." They gave procainamide to nine patients with myotonia because of previous work that they cite with procaine in myotonia and the current knowledge that oral procainamide was being used satisfactorily to control hyperirritable cardiac foci. Good results in the "voluntary contraction myotonia" was obtained in eight of their patients, but no appreciable effect was obtained in "percussion myotonia" and only an incomplete alleviation was obtained in "needle myotonia." Though Floyd, Kent, and Page[2] found a depression of "percussion myotonia" when procaine was injected into a muscle in a single patient, our findings are similar to Geschwind and Simpson's in that we found but little alteration of the "percussion myotonia." Geschwind and Simpson also found no evidence of developing tolerance to the drug and no serious side-reactions.

Although 2 gm. daily would appear to be the minimal dose for alleviation of the myotonia, generally 3-4 gm. has been required for maximal relief of this sign. The drug is apparently safe when proper, simple precautions are followed. We encountered no change in the hemogram, although agranulocytosis has been reported.[3] We observed no tolerance to the drug and no new side-reactions while the patient was being maintained on the medicine.

Conclusions

Procainamide seems significantly to reduce "voluntary contraction myotonia" but has little or no effect on "percussion myotonia."

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Society Transactions

NEW YORK NEUROLOGICAL SOCIETY AND NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY

Abner Wolf, M.D., President, New York Neurological Society, Presiding
Joint Meeting, Oct. 9, 1956

Prenatal Infections of the Central Nervous System: Presidential Address. DR. ABNER WOLF.

Presumed Role of Glial Cells. DR. SAUL KOREY.

A significant concentration of glial cells from white matter of the brains of lambs has been achieved by means of differential sedimentation. The cells are partially damaged, since the mechanical means of separating them from the substance of the white matter necessarily cuts the processes of the glial cells. In addition, the hyperosmolarity of the media used causes extraction of both water and water-soluble constituents from the cells to some extent. Within these limitations the procedure achieves the isolation of about 10% of available glial cells in the white matter, with a purification of about 15 times. The nucleotide, lipid, and protein constituents of the cells were discussed as means of reference for further work. The cells respire with a QO_2 of about 5.

Discussion

DR. ABNER WOLF: Dr. Korey has given us a very stimulating review of investigations of the role of neuroglia in the central nervous system. He has presented the fruits of his first attempts to isolate glial cells, and we all hope, with him, that this will open the path to further investigation of their functions. The first great wave of interest in, and accumulation of data on, the neuroglia was that of the famous German school of neuropathologists, active at the turn of the century and just before it. The Spanish school of neuroanatomists then made further historic contribution to our store of knowledge in this field. Now, the American and English schools of neuroanatomy, neuropathology, and biochemistry are attacking the problem. Dr. Korey is one of those who promise to contribute greatly.

Dr. Zimmerman, may I call on you for discussion?

DR. HARRY M. ZIMMERMAN: I don't know why Dr. Wolf calls on me, as a morphologist, except in retribution for Dr. Korey's essay in the field of morphology, and I presume he wants me to talk about biochemistry! Actually, some years ago my colleagues and I tried some of the work which Dr. Korey did and were a little discouraged from the morphologic standpoint. We were not certain how much cytoplasm those cells really contained. Moreover, we were worried as to whether the damage produced by saturated sucrose interfered with metabolic processes sufficiently to prevent accurate analyses of the kind described by Dr. Korey. Therefore, we felt that unless we analyzed purely for lipids and proteins—in other words, the dead constituents of the cell—the results would be meaningless. We did not think vital-biochemistry studies could be done, and so we abandoned the field to someone who is much abler than we are, and we shall wait the two years for Dr. Korey to come back and tell us what this all means. Much of what he has told us has to do with the proof that these cells still have cytoplasm. I should like to know: What of it?

DR. FRITZ CRAMER: In contrasting this method with morphologic studies and tissue cultures, it was thought that no true inferences can be drawn from them as to "respiration." Are these cells or these cultures living, and is Dr. Korey therefore drawing inferences as to respiration on the part of functioning, living cells? I did not get that point.

DR. SAUL KOREY: In answer to Dr. Cramer: These cells were harvested from the white matter by removing by suction all the overlying gray matter. Then we have the strips of white matter; we homogenize this in a particular way and centrifuge it. After that we keep filtering it through various screens until we get to a point where we can centrifuge the suspension in a density gradient; after we centrifuge at 18,000 g, the myelin fragments in this medium rise to the surface and the cells are left at a lower interface. We are able to remove the cells after we remove the myelin.

When the cell respires, it is sufficient to start with. I would say that the carbonic anhydrase is very high in white matter, for example. At this particular moment we are in a position to see whether it is a glial component. There are two problems: The first is what we study, whether it is a synthetic group or a hydrolytic group of enzymes. If we start with acetate and are building

up long-chain molecules or cyclical compounds, there is a synthetic group of enzymes involved. If we are studying enzymes that cleave an ester down into an acid and alcohol, then these enzymes which are hydrolytic are easier to retain and examine in such a preparation. Carbonic anhydrase, which is a "simple" system, may be preserved in our preparation. The second problem is whether what we observe relates back to the tissues in situ. There is no simple answer to that.

Experimental Cryptococcosis (Torulosis). DR. SEYMOUR LEVINE.

Experimental cryptococcosis was produced by subcutaneous, intracerebral, and intraperitoneal inoculations, using three strains of Cryptococcus neoformans. The subcutaneous lesions were characterized by early leukocytic response, abscess formation, encapsulation, and healing, and only occasional instances of dissemination. Brain lesions were characterized by proliferation of the yeast cells to form large lesions, with little inflammation and with universal dissemination. More inflammation was noted in the meninges; but here, too, the reaction was weak and irregular. Intraperitoneal inoculations were attended by an intermediate degree of inflammatory response (usually most marked in the liver) and were also intermediate with respect to dissemination and lethality. The predilection for the brain in cases of dissemination was thought to be directly related to the paucity of inflammatory response in cerebral tissue.

The presence of healing subcutaneous cryptococcal abscesses failed to confer active immunity against subsequent intracerebral challenge.

The inflammatory response to subcutaneous inoculation of C. neoformans was abolished by cortisone, and, to a slighter extent, by x-radiation. This was accompanied by a marked increase in dissemination.

Discussion

DR. HARRY M. ZIMMERMAN: The question I asked Dr. Korey, of course, I asked Dr. Levine in my own laboratory, and Dr. Levine has already told you the reason that these experiments were undertaken. We were not interested in infecting a group of mice with an organism that is uncommon in this part of the world in order to see the results in rodents; we were more interested in what to do about these almost universally fatal cases of cryptococcosis we see in man. In the past 10 or 12 years we have had 10 cases, and we were convinced that the fatal outcome had something to do with a lack of tissue response to the infecting organism. It was for this reason that Dr. Levine undertook to isolate the polysaccharides from the organism in cultures, and for weeks and months my laboratory was jammed with flasks in which he was growing them in order to get capsular material. He did not tell you that many mice were injected with the capsular material without any immunity being produced in the animals, and this, in order to find out why capsular material would not produce immunity, led him to the experimental results which he presented. I shall not elaborate on them, because I think Dr. Levine has adequately done so.

DR. SAUL KOREY: I should like to ask Dr. Levine whether he feels that this reactive difference in cerebral tissue, where the vascular tissue contains enough leukocytes even as compared with the skin, is an immunologic difference, or whether it is due to there being a great deal of cortisone-like material around in the brain to prevent the reactive response, or does he feel there is an immune difference in the actual leukocytic series in the brain?

DR. SEYMOUR LEVINE: I wish I could answer that question. It is obviously the question that I have been asking myself every time I studied the slides. I noticed in my sections that when leukocytes did appear in the brain they were often in relation to the choroid plexus or the meninges, and I wonder whether there is not a quantitative difference in the amount of blood supply or the number of connective tissue cells that are available in the brain, or perhaps in some other factor in a quantitative rather than a qualitative sense. That is the only possible answer I can offer.

NEW YORK NEUROLOGICAL SOCIETY AND NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY

Rollo J. Masselink, M.D., Secretary, New York Neurological Society, Presiding
Joint Meeting, Dec. 11, 1956

The Organic Mental Syndromes: Elementary Consideration. DR. SAMUEL THOMAS.

A definition is given for the organic mental syndrome. Productive and reductive symptoms are distinguished and exemplified in disturbances of perception, attention, awareness, orientation, memory, behavior, personal habits, judgment, conduct as a whole, content and sequence of

thinking, character, and individuality. Symptoms of certain special conditions are assigned their places in this list. Further psychological factors are mentioned briefly. The reductive symptoms are considered more characteristic of the organic mental syndromes than the productive.

Discussion

DR. THOMAS K. DAVIS: I should like, first, to commend Dr. Thomas for giving such a good paper. I am critical of the title—not a serious criticism indeed.

If we use elementary, as it sometimes is used, to imply incompleteness and the mere rudiments of a topic, his titling does disservice to his production. No doubt he is using elementary in the more exact sense—as that which deals with the elements of a subject.

I think Dr. Thomas has demonstrated that he is a neuropsychiatrist who writes a paper from what he has observed, and not from what he has read. His is to my mind an original approach. Another thing which I would like to commend is his excellent choice of adjectives to define the various elements as he goes along.

Incidentally, one notes the happy absence of psychiatric clichés.

Calcification and Ossification of the Spinal Leptomeninges with Myelopathy and Radiculopathy. DR. FRITZ CRAMER and DR. JAMES W. CORRELL.

Whereas small calcifications in the leptomeninges are met frequently and are of no clinical significance, this report describes seven cases with massive calcifications in which there was undoubted clinical significance. Despite calcific masses 1 or 2 cm. by several centimeters long and several millimeters thick, they were not revealed by x-rays. On lumbar puncture a manometric block was often present, but spinal fluid protein was low. Myelograms revealed atypical defects or a block. The neurologic symptoms corresponded to the location of the calcifications; i. e., they were myelitic or radicular in type.

The etiology of the calcifications or ossifications was probably diverse. Among probable causes were direct trauma, in one case; bacterial meningitis, in one case, and, in another case, three spinal anesthesias in close sequence, each with sequelae. The only other finding of possible etiologic significance, occurring in the majority of cases, was the presence of degenerative osteoarthropathies. In two cases there was early calcification of a thoracic intervertebral disk.

Two types of calcified and ossified leptomeningeal thickening were seen. In one type the ossification occurred over the spinal cord, while in the other type nerve roots were compromised. The neurologic symptoms corresponded to the location of the calcification, i. e., were myelitic or radicular in type. The calcific masses in themselves are capable of producing symptoms by virtue of their space-taking nature. They probably both cause direct pressure upon the new structures involved and also compromise them secondarily by impairing local vascular circulation.

In these cases surgical exploration should be carried out. When the lesions involve the nerve roots, improvement follows; but when the spinal cord is affected, the results are less encouraging.

Discussion

DR. JACK LONDON: I should like to ask how thick those plaques were and where the bone comes from. What was the origin of the bone you talked about?

DR. SAMUEL FEDERMAN, Brooklyn: Were any of your cases diagnosed preoperatively?

DR. ROLLO J. MASSELINK: I should like to ask if, on review of the x-rays after the diagnosis was established, you were able to pick up the calcification that was missed preoperatively.

DR. FRITZ CRAMER: Dr. Wolf was going to discuss the matter of the origin of the calcification, and, in his absence, I will undertake to discuss it as I understand it from the literature. Most of the reports on this condition are of French and German origin, and, interestingly enough, they ascribe the primary meningeal reaction and subsequent calcification as due mostly to syphilis, particularly, tabes. Other conditions in which one finds some thickening of the arachnoid, sometimes with calcification, are long-standing disturbances of the neuraxis with secondary degeneration, the heredodegenerative diseases, and syringomyelia, as well as in any localized inflammation, arthropathy, including diseases of the intervertebral disks, and tumefaction outside the dura. I think that in our cases there were perhaps different etiologies, but it is of interest that we should have had one case in which previous direct trauma in the area was undoubtedly an etiologic factor in causing calcification, and that we found no syphilis and no reaction to syphilis in any of our cases. Those patients in whom the spinal cord was involved probably had a different etiology from those in whom the arachnoid was involved near the nerve roots.

The most appealing explanation I have come across from the German and French literature is that the calcification is located dorsally because of the compartmentation, so to speak, of the arachnoid space. Posteriorly in the midline is the so-called ligamentum posticum of Schwalbe, connecting the pia and the arachnoid. Then out laterally are the normal webs between the arachnoid and the pia, connecting them with the spinal

cord, dentate ligament, nerve roots, and blood vessels. In certain instances, let us say the intramedullary diseases of the spinal cord, there are abnormal products of the metabolism and the catabolism of the cord, and these are of a different nature from the normal protein within the spinal subarachnoid space. In the case of a spinal cord tumor causing a block, with stagnation and increased protein, the protein is virtually pure plasma, exuding from tortuous veins. We do not find massive adhesions; we may find some adhesions and flecks of calcium, but adhesive processes are not the typical picture. In the adhesive conditions we do not find an increased protein. In them, it may well be that products of degeneration arising within the diseased spinal cord cause an irritation of the leptomeninges, which then results in thickening, and eventually in calcification.

Now to come to the questions which I may not have answered: 1. The thickness of the plaques was 1 to 2 to 5 mm. 2. The bone is simply the end-stage in the laying down of calcium in the thickened arachnoid. 3. A preoperative diagnosis of calcification was not made in any of our cases. The one which was cited in the German literature of recent origin, in which they showed two roentgenograms and a pathologic specimen, revealed the calcification beautifully.

DR. ROLLO J. MASSELINK: In looking back over the x-rays, could you see the calcification?

DR. FRITZ CRAMER: In looking back over the x-rays in our personal cases, we may see some faint signs of the calcification, but they are not sufficiently convincing to make the diagnosis possible.

The Dependence on Narcotic Drugs. DR. SANDOR RADO.

To achieve clarity, we have separated the pathology of drug dependence from the pathology of the underlying disorder, applying to both the insights of adaptational psychodynamics. In this light, drug dependence is seen to be a self-inflicted process of miscarried repair; it transforms realistic self-government into narcotic self-government. Utilizing our previously suggested concepts of narcotic pleasure-effect, narcotic elation, and narcotic craving, we have shown that both elation and craving are interdependent manifestations of a narcotic delusion of grandeur elicited by and anchored in the pleasure effect of the drug. This delusion is explained by the bribing action effortless pleasure has on the system of hedonic self-regulation, which forces the organism to repeat this type of pleasure again and again. From this malignant pathology we deduced the plan for rehabilitation: withdrawal of the drug; reconstructive psychoanalytic therapy, whose goal is to control the potential dangers of suicide and relapse and, whenever feasible, to eradicate the underlying disorder. Finally, attention was called to the need to advance the physiology of pleasure, which may well hold the key to the patient's biochemical immunization against the intoxicating pleasure-effect of narcotic drugs.

Discussion

DR. DANIEL M. SHAPIRO: Dr. Rado's contribution illuminates a challenging problem, the specific effects of narcotics on the motivational structures of the addict, and the unique significance it has in his life.

Ten years ago, when I was a resident at the U. S. Public Health Service Hospital for Treatment of narcotic addicts at Lexington, Ky., I first became familiar with Dr. Rado's early brilliant efforts to penetrate the maze of addiction. Tonight's reformulations in terms of adaptational theory are clear and penetrating; they should advance our solution of the knotty problem of the treatment of the addicted person.

PHILADELPHIA NEUROLOGICAL SOCIETY AND MEDICAL SOCIETY OF THE DISTRICT OF COLUMBIA, SECTION OF NEUROLOGY AND PSYCHIATRY

Ernest A. Spiegel, M.D., Philadelphia, and Stacy L. Rollins Jr., M.D., Washington, D. C., Presiding
Joint Meeting, Nov. 2, 1956

Acute Idiopathic Cerebellar Disorders of Childhood. DR. GABRIEL A. SCHWARZ, DR. GERALDINE A. KING, and DR. HARRY SLADE (by invitation), Philadelphia.

The authors made a clinical report on eight children who developed a markedly ataxic gait, truncal and head ataxia, action tremor, and incoordination of the extremities, nystagmus, and/or scanning speech. Although some of the children also had involvement of the cerebellum, brain stem, and/or spinal cord, the predominant disorder seemed to be due to cerebellar deficit. These children had no significant previous illnesses, little fever, and, frequently, a normal cerebrospinal fluid, and many of them made a rapid and complete spontaneous recovery. Persistent ataxia and residual behavior disorders occurred in a few cases. All attempts to establish the etiology in these cases failed.

It is suggested that such cases represent a toxi-infectious process of probably variable origin, with the cerebellum or its systems as the major or only target organ. The chief significance of this relatively benign form of cerebellar disorder in children is its differentiation from cerebellar tumor. Ventricular tap and ventriculography may be necessary to establish the diagnosis.

Discussion

Dr. G. Milton Shy, Bethesda, Md.: There is very little that any clinician can add to what the authors have already presented in the differential diagnosis. Among the diseases which have to be discussed are, first, the hereditary, and second, the demyelinating, types.

We commonly think of cerebellar ataxia as having no remissions or exacerbations and as a chronic progressive disorder. We have recently been screening demyelinating diseases and cerebellar ataxia at the National Institutes of Health with this particular point in mind, and have found definite exacerbations and remissions in one-quarter of our cases. The second point in demyelinating disorders is the possibility that they can fall in the metachromatic group described by Norman and Greenfield.

The one disorder in the cerebellar system which Dr. Schwarz did not mention is the phenomenon of myoclonus.

I do not know what type of seizures the authors' patients had, but by myoclonus I mean a migrating seizure pattern, which may be first in one extremity, then in the face, and then in another extremity—never symmetrical. If it is symmetrical, we call it myoclonic epilepsy. These seizures have been shown in the last five or six years to be related to disorders predominantly of the cerebellar system, and this has been brought forth by Greenfield, in England, van Bogaert, in Belgium, and others.

We recently have had three infants who had cerebellar ataxias with a congenital history who came in with progressive myoclonus seizures and died. I should like to show you some of the pathology.

(Slide) This is merely to show one folium of the cerebellum, although the whole structure is wiped out. In this case the posterior columns of the cord and the folia of the cerebellum were completely gone, and there was root injury. Spared, strangely enough, was the vermis.

(Slide) This is the metallic stain to show the so-called torpedoes which occur on the end of the Purkinje axons in these particular disorders.

(Slide) This is to show that it sometimes pays to use a combined myelin and fat stain. You can see the fat being picked up in the various cells throughout the system.

I would like to call it to your attention that the hereditary group of cerebellar ataxias may be extremely lethal in a newborn infant, particularly at and up to 6 months of age; and it may frequently present itself as so-called myoclonus epilepsy.

Dr. Ernest A. Spiegel, Philadelphia: I should like to ask a question of the authors: What relationship does their syndrome have to that described by Bárány, in which a tumor of the cerebellopontine angle is sometimes imitated by a more or less circumscribed arachnoiditis?

Dr. Nathan S. Schlezinger, Philadelphia: One gets the impression, in listening to this paper and the description of cases, that the etiology might be varied. I was wondering in terms of my own experience, which is much more limited, whether acute infectious mononucleosis was considered in any of these cases, or whether it was excluded by studies? I had occasion to see one child who did have a picture predominantly of cerebellar involvement in which that etiology was verified.

Dr. Gabriel A. Schwarz, Philadelphia: We realize that there may be many explanations for this group of cases. Certainly, the idea that they may represent an early form of one of the demyelinating diseases was seriously considered. I suppose the answer would be to follow these patients over a long period of time. We did follow some of them for quite a long time. One of them did develop seizures years later, but so far we have not had any of them develop any of the phenomena that Dr. Shy has described in his cases.

Dr. Spiegel asked whether or not this disorder was related to a circumscribed arachnoiditis in the cerebellopontine angle. The syndrome we saw was not that of the cerebellopontine angle. As a matter of fact, the disorder in these cases resembled more a syndrome of the flocculonodular lobe, because the patients' greatest difficulty was in static equilibrium.

As to Dr. Schlezinger's remark about the variety of causes, we have been struck by that idea very forcibly and have put our efforts into studying recent cases to find the answer from the standpoint of various etiologic factors.

I do not believe that tests for infectious mononucleosis were done in our cases. In the past month we had another of these cases in the University of Pennsylvania Hospital. Our patient was a little girl of 3 years who went through this same cycle of ataxia and peculiar seizures. Incidentally, we have never seen the fleeting variable seizure pattern or myoclonus which Dr. Shy mentioned.

On this child, we did run tests for infectious mononucleosis, and we did not find it. As a matter

of fact, we measured her blood lead content, and it was normal. The virus laboratory at Children's Hospital tested her for lymphocytic choriomeningitis, mumps, lymphogranuloma venereum, Q fever, adenovirus, poliomyelitis virus 1, 2, and 3; they gave her complement fixation tests for herpes simplex, cold agglutination titer determinations, and so forth, and all of them were entirely within normal limits. Further work in these directions will be necessary before the causes in these cases are apparent.

Neurological Aspects of Porphyria. Dr. Richard W. Naef (by invitation), Dr. Richard G. Berry, and Dr. Nathan S. Schlezinger, Philadelphia.

Two cases are presented of acute intermittent porphyria with involvement of the nervous system. The clinical picture was that of a progressive peripheral polyneuropathy, predominantly motor in its manifestations. In one case there were manifestations of diffuse cerebral involvement. Both patients died of respiratory paralysis. The pathological changes were those of a nonspecific parenchymatous neuropathy with associated spinal root involvement of a less severe degree. In the central nervous system there was axonal chromatolysis of cells in the anterior horns and vagal nuclei, with nonspecific changes consistent with the respiratory death.

The pathophysiology is considered to be an abnormality in the metabolism of porphyrin compounds. The resultant disturbance of intracellular enzymes is reflected in widespread functional changes in the nervous system.

Discussion

Dr. Francis M. Forster, Philadelphia: The authors are to be congratulated on their scholarly paper, dealing with a very difficult subject. It shows great clarity and presents good illustrations of the cerebral and peripheral nerve involvement which occurs in patients with porphyria.

In reading the manuscript, I experienced some déjà vu phenomena in regard to the second case, which I recall from my own time at Jefferson Hospital.

Dr. Naef very ably handled the neuropathological findings and has been forthright in discussing their absence in the central nervous system in this disease. The absence of neuropathological findings does not mean that there are none; it merely means that the changes are chemical and have not yet evolved to the point at which the more subtle changes appear. It would seem entirely reasonable that Dr. Naef's premise of enzyme chemistry involvement in these diseases is the correct one. The direction in which basic neurology is now evolving is definitely in the field of neurochemistry. This has been exemplified by the setting up of a section on neurochemistry in the American Academy of Neurology. Studies such as this of Dr. Naef's, ranging from clinical to neuropathological to biochemical, hold a bright hope for the future.

Dr. Valentine Anthony Ujhely, Veterans' Administration: I would like to mention a case of suicidal attempt with Photodyn, also called Fluodyne (hematoporphyrin), which in a large dose could produce acute toxic porphyria. In 1946 a 21-year-old woman with a schizoaffective phobic reaction (and only superficially cooperating in psychoanalysis), because of deep hatred toward her mother and as a protest against being borne by her, drank a cousin's Photodyne solution, which was supposed to be taken in gradually ascending doses (and returning gradually to 10 drops a day). Our patient drank this cousin's remedy, a whole ounce in one gulp. Neurologically she developed only a transient partial aphonia, somnolence, mild amblyopia plus transient diplopia with erythropsia, and abdominal colicky pains, radiating into the lower extremities, without any peripheral motor paralysis but with somewhat reduced tendon reflexes. Psychologically she experienced a sudden panic of impending annihilation, which evoked a salutary shock, and this reactivated her will to live.

Tetraethylammonium chloride (Etamone chloride) being then nonexistent, I asked her family physician to inject liver extract intramuscularly and to give her thiamine chloride, nicotinic acid, and ascorbic acid; I also requested her abstention from sunlight. In five days the patient came to the psychiatrist; during a prolonged psychocathartic session, she revealed despair over a discharging, and at times malodorous, sinus at her naval, because of which she dreaded to be courted or married, inasmuch as she feared rejection. After surgical removal of a persistent omphalomesenteric (vitelline) duct, there was a dramatic recovery from her psychoneurosis; she began to socialize, obtained a secretarial position, and within a year was happily married. She now has a young son.

Dr. John R. Bower, Reading, Pa.: Most cases of porphyria appearing in the literature, including those presented here, terminate fatally. It must be remembered that all these patients have had a long history of varied, protean complaints, with missed diagnosis prior to the fatal episode.

I have been following one patient with porphyria since October, 1940. She has had "bilious attacks" since childhood, which disappeared with the onset of epilepsy. There was questionable papilledema, but no definite objective findings. Air studies were refused. In March, 1947, she developed definite signs of increased

intracranial pressure, followed by craniotomy for release of a block of the iter. In June, 1948, there was severe abdominal pain, followed by appendectomy. In July, 1948, she had a suspected intestinal obstruction. In October, 1948, she developed the Guillain-Barré syndrome. In August, 1953, there was recurrent pain, but gastrointestinal and kidney studies were negative. In September, 1953, she had weakness of muscles supplied by the right ulnar nerve. In August, 1956, she again had severe abdominal pain. Porphyria studies at that time were positive, and for the first time the true nature of her basic pathology was recognized. She was put on chlorpromazine (Thorazine) and riboflavin and within 36 hours was symptom-free.

DR. GABRIEL A. SCHWARZ: Were there any changes in the striated muscles in this case? If there were, was it felt that such changes were primary in the striated musculature, or were they secondary to the peripheral nerve changes?

The second question I would like to ask pertains to the changes in the peripheral nerves themselves. I suppose it is hard to know which comes first, but I wondered whether in their observations the authors felt that the primary effect in porphyria was on the axis cylinders, or on the myelin sheath, or perhaps even the Schwann cells? Could they tell this at all from their histological sections?

I was interested in one of the other discusser's remarks about hematoporphyrin (Photodyn). I suppose most of you know that in the literature there is a case reported by Dr. Melvin Thorner in which a peripheral neuropathy developed with the use of Photodyn.

DR. RICHARD W. NAEF, Philadelphia: As to the changes in muscles, we can add nothing, since no specimens of muscles were taken for study in either case. The changes in muscles seen associated with severe neural lesions are those typical of neural atrophy, as reported recently by Adams, Denny-Brown, and Pearson.

The changes in the nerves, we thought, were predominantly in the myelin sheaths, in the degeneration of the myelin, because that was a much commoner finding than the axis-cylinder loss. However, there were spots in which the axis cylinders were damaged, but in most sections they were associated with a greater degree of degeneration.

As to the abdominal pain, the cause has allegedly been due to a disturbance in the autonomic innervation of the musculature of the intestine, and the pain can actually be stopped by using blocking agents and by splanchnicectomy.

In abdominal x-rays of our cases, the intestine can be seen to be dilated with segmental constriction, as has been reported by others. This segmental spastic phenomenon is believed to be the cause of the abdominal pain and evidence of there being a disturbance of autonomic innervation.

No endings of the nerves in the skin were actually examined. The nerve endings in the intestine were not examined.

Pallidotomy and Pallidoamygdalotomy in Certain Type of Convulsive Disorders. DR. HENRY T. WYCIS, DR. HENRY W. BAIRD III (by invitation) and DR. ERNEST A. SPIEGEL, Philadelphia.

The authors gave a preliminary report on the effect of pallidal lesions (pallidotomy) or combined lesions of the pallidum and amygdala (pallidoamygdalotomy) upon major and minor convulsions in a group of epileptic patients selected according to the following criteria: (1) ineffectiveness of anticonvulsive medications, and (2) demonstration of seizure discharges in the basal ganglia, for which a slight sedation produced by tranquilizing drugs (reserpine, meprobamate, chlorpromazine) was of value. Originally only relatively small lesions limited to the anterior part of the pallidum were produced. Since our stereoencephalotome permits us to apply the apparatus repeatedly in exactly the same position, the size of the lesion can be increased in stages. In two cases small bilateral pallidal lesions proved insufficient, and in one case unilateral pallidoamygdalotomy reduced the frequency of the seizures but did not stop them completely. In three cases the seizures could be stopped or markedly reduced for observation periods ranging from 7 to 21 months. In the seventh case the postoperative period with cessation of the seizures (over one month) is too short to allow definite conclusions. In the three favorably responding patients, the major tonic-clonic convulsions, as well as the minor seizures, were controlled by the operation, indicating that forebrain mechanisms may also participate in some types of minor attacks. This applies particularly to the salaam convulsions (astatic seizures of Lennox), an experience that seems to indicate that the basal ganglia play an important role, particularly in the pathogenesis of this type of minor seizures. In two of the clinically improved cases, the scalp EEG also showed a tendency toward normalization in that the seizure discharges disappeared or became much less frequent and were reduced in voltage. These findings suggest that at least in a part of these cases not only the peripheral muscular manifestations of centrifugal impulses passing through the basal ganglia but also the effect of subcortical epileptogenic foci upon the functional state of the cortex was influenced.

Discussion

DR. JONATHAN M. WILLIAMS, Washington, D. C.: To me, two things in this study are of

great interest: The first is the fallibility of scalp, and even cortical, electroencephalographic recordings as a means of localizing deep abnormalities, and the second is that already benefit has accrued to those selected patients in whom the location of the disease has been so precisely pinpointed by the Wycis-Spiegel stereoencephalatome.

I am particularly interested in the attention the authors have given to the amygdaloid nucleus. Several years ago Freeman and I devised a theory to explain persisting hallucinations and postulated that the amygdaloid nucleus played a part in the circuit necessary for the continuation of these phenomena. We selected five patients for amygdaloidectomy. The results in general were disappointing, and we operated in no more cases. However, from the ruins of our idea I think some salvage was gained. Of the five cases in which we operated, hallucinatory experiences developed largely from organic brain disease in two, and in these two cases only were the hallucinations reduced. This suggested a possible relationship between these hallucinations and psychomotor epilepsy. In my limited experience, with another five cases of psychomotor epilepsy, I have included the nucleus in all temporal lobe resections and have had complete and total relief in four of the five cases, while in the fifth case grand mal attacks have continued but with less frequency.

Drs. Wycis, Baird, and Spiegel are to be encouraged in their studies of the participating role the basal ganglia play in the production of epilepsy of various kinds. The stimulus they have afforded to others working with epilepsy has indeed been as helpful as the contributions that they themselves have made.

Dr. David J. La Fia, Philadelphia: I should like, first, to ask Dr. Wycis if he has any idea why the seizures returned. Is it a quantitative thing? It is easy for me to do some armchair thinking; but what really happens?

Second, after you make your lesion, do you record immediately? I should like to know what criteria you use for knowing that you have an effective electrolysis, and over what sort of area. We know it is very difficult to destroy a pinpoint area even with the new radiofrequency currents that Sweet uses. Also, do you have any pathological material to confirm some of your lesions?

Dr. Gabriel Schwarz, Philadelphia: I would like to ask something from the purely clinical standpoint. After you perform these pallidotomies and pallidoamygdalotomies, are there any residual clinical findings, neurological or psychological, which are the result of the destructive lesions?

Dr. Ernest A. Spiegel, Philadelphia: I wish to express my thanks to all the discussers, particularly Dr. Williams. The effect of azocyclonol (Frenquel) has not been studied as yet. The reappearance of seizures in some of these cases is understandable if one considers that only incomplete lesions were produced, in some instances only pallidal lesions, in others only unilateral lesions of the pallidum and amygdala. Since we insert recording electrodes before the operation, the x-ray studies of the patient after insertion of the electrodes and comparison of these films with those obtained preceding the operation and in which the ventricular system is visualized permit one to check the position of the electrodes. Since our mortality was zero, we have no autopsy findings. Recently we have studied the variability of lesions produced by radiofrequency current, but have found it even higher than that of lesions produced by electrolysis. Regarding changes in behavior following bilateral pallidotomy, there was in one patient a transitory reduction of initiative. In children an improvement of their mental status could be noticed, which was probably due to the reduction of the number of seizures, and thus of the secondary effect of the convulsions upon the brain, and also to the reduction of anticonvulsant medication.

Abstracts from Current Literature

Edited by Dr. Bernard J. Alpers

Physiology and Biochemistry

Electric Activity of the Olfactory Bulb in Man. C. W. Sem Jacobsen, M. C. Petersen, H. W. Dodge Jr., Q. O. Jacks, J. A. Lazarte, and C. B. Holman, Am. J. M. Sc. 232: 243 (Sept.) 1956.

In the course of frontal lobe operations on 17 psychotic patients, electrodes were placed in various parts of the olfactory bulb. Stimulation of the nasal mucosa was carried out by blowing measured amounts of aromatic substances into the nose. It was found that there was a resting or background electrical activity of 36-40 cps. of constant amplitude. The potentials evoked by stimulation of the nasal mucosa consisted of rhythmic sinusoidal waves of 25-39 cps. The response to a single aromatic substance showed a wide range of frequencies rather than a single frequency, but the amplitude of response could be altered by varying the intensity of stimulation. Occasionally a strong blast of an effective odor might initially produce an inhibitory effect of the background activity for a second or so, after which the usual response appeared. Prolonged stimulation also caused a decrease of amplitude of response after 10-100 seconds. If, during this period of decreased reactivity, another aromatic stimulus was used, the response to the second substance was immediate and of maximal amplitude.

Berlin, New York.

Carbohydrate Metabolism in Brain Disease: VII. Effect of Glutathione on Carbohydrate Intermediary Metabolism in Schizophrenic and Manic-Depressive Psychoses. M. D. Altschule, D. H. Henneman, P. D. Holliday, and R-M. Goncz, A. M. A. Arch. Int. Med. 99:22 (Jan.) 1957.

In view of the fact that patients with schizophrenia and manic-depressive psychoses display disorders in intermediate carbohydrate metabolism, it was decided to administer glutathione (a co-enzyme which plays a role in carbohydrate metabolism), which is low in these psychoses and which shows in vitro antagonism to certain hallucinogenic agents. Five patients, one schizophrenic and four with depression, were given intravenous glutarate, with resultant consistent improvement of previously abnormal blood glucose and, lactate, citrate, pyruvate, and α-ketoglutarate curves, reflecting more normally rapid utilization of ketoacids. The clinical condition of the patients showed very transitory or negligible change, except for one depressed patient, whose improvement lasted several months. Untoward effects consisted of hypotension, bradycardia, and epistaxis and were related to too rapid a rate of administration of glutathione. No correlation of biochemical and clinical changes was possible in these cases.

Parsons, Montrose, N. Y.

Carbohydrate Metabolism in Brain Disease: VIII. Carbohydrate Metabolism in Wernicke's Encephalopathy Associated with Alcoholism. M. Victor, M. D. Altschule, P. D. Holliday, R-M. Goncz, and A. County, A. M. A. Arch. Int. Med. 99:28 (Jan.) 1957.

Thiamine deficiency states, such as Wernicke's encephalopathy, result in altered carbohydrate metabolism. Thiamine pyrophosphate is a co-enzyme essential to the oxidation of pyruvic acid, and thiamine deficiency states, such as Wernicke's encephalopathy, show elevated pyruvate levels, which, along with the ocular changes, ataxia, and somnolence (but not the memory disturbances), may be reversed by the administration of thiamine. These observations were checked by the evaluation of blood glucose and blood lactic, pyruvic, citric, and α-ketoglutaric acid levels in fasting state, following the administration of dextrose and then following the administration of thiamine on a group of 17 patients with Wernicke's syndrome and on 17 controls. Most patients with Wernicke's syndrome showed elevation of all blood carbohydrate constituents (pyruvic acid) in the fasting state before treatment. Administration of dextrose resulted in further rise (especially of pyruvic and α-ketoglutaric acids) and a relatively slow fall following thiamine administration. It was noted that the clinical response to thiamine

was prompter than was the biochemical, the latter being accelerated by the institution of a fully balanced diet in addition to the therapeutic doses of thiamine.

PARSONS, Montrose, N. Y.

CARBOHYDRATE METABOLISM IN BRAIN DISEASE: IX. CARBOHYDRATE METABOLISM IN THE CHRONIC ALCOHOLIC PSYCHOSES. M. D. ALTSCHULE, M. VICTOR, and P. D. HOLLIDAY, A. M. A. Arch. Int. Med. 99:40 (Jan.) 1957.

A group of four patients with Korsakoff's psychosis and another of five patients with chronic alcoholic hallucinosis received studies of fasting blood levels of glucose and lactic, pyruvic, citric, and α-ketoglutaric acids, after which 100 gm. of oral glucose was administered and three-hour curves for blood levels of these substances were determined. Comparisons with values previously derived for normal subjects disclosed that both types of psychosis displayed the same abnormalities, characterized by normal fasting levels with decreased glucose tolerance curves (elevated values following glucose administration). This pattern of response is identical with those seen in patients with schizophrenia and manic-depressive psychoses, as well as in nonpsychotic patients with certain neurological disorders (i. e., multiple sclerosis) and in severe liver disease and pernicious anemia.

PARSONS, Montrose, N. Y.

CEREBRAL HEMODYNAMICS AND METABOLISM IN ACCIDENTAL HYPOTHERMIA. W. R. EHRMANTRAUT, H. E. TICKTIN, and J. F. FASEKAS, A. M. A. Arch. Int. Med. 99:57 (Jan.) 1957.

Two patients with accidental hypothermia were subjected to studies of cerebral blood flow by the nitrous oxide technique of Kety and Schmidt. Both patients demonstrated decreased CBF (cerebral blood flow, cc/min/100 gm. of brain) and $CMRO_2$ (cerebral oxygen consumption, cc/min/100 cc. of brain) probably on the basis of a demonstrated increase in cerebral vascular resistance while in the hypothermic state. Inasmuch as the mean arterial blood pressure remained normal (in contrast to previous studies of hypothermia induced by trimethaphan camphorsulfonate [Arfonad], thiopental [Pentothal], and chlorpromazine, in which the mean arterial blood pressure was reduced), the authors hypothesize that the increased cerebral vascular resistance may be due to increased blood viscosity or to cerebral vasoconstriction due to the hypothermia. Both patients displayed normal cerebral blood flow findings upon recovery.

PARSONS, Montrose, N. Y.

THE SEPARATION OF SPHINGOLIPIDES BY ADSORPTION CHROMATOGRAPHY. B. WEISS, J. Biol. Chem. 223:523, 1956.

A method is presented for separation of small amounts of sphingolipides of the brain by chromatography on a silicic acid column. The sphingolipides of beef spinal cord and monkey brain gave similar profiles but wide quantitative differences in each fraction. A carbohydrate-containing fraction was alone present in monkey brain. Kerasin and phrenosin and a third glycosphingoside containing two atoms of nitrogen per mole of hexose and probably lignoceric acid were separated. Two kinds of phosphosphingosides were found, with one of them containing arachidic acid. One fraction from monkey brain contained at least one phosphorus-containing and two carbohydrate-containing components, probably gangliosides. Perfusion of monkey brain with acetate-1-C^{14} or octanoate-1-C^{14} results in labeled sphingolipides, which are found in Band IV. Octanoate-1-C^{14} added to unlabeled sphingolipides appeared with the glycosphingoside in Band I.

PAGE, Cleveland.

SIZE AND SHAPE OF RADIOSENSITIVE ACETYLCHOLINESTERASE UNIT. I. SERLIN and D. J. FLUKE, J. Biol. Chem. 223:727, 1956.

Radioactive cobalt Co^{60} gamma rays, electrons, protons, and alpha particles were used to irradiate acetylcholine esterase from the electric organs of eels. Inactivates were found experimentally related to the dose. The unit of the enzyme which is radiosensitive is indicated to have a molecular weight of 105,000 and to be nonspherical. Assuming a cylindrical shape, the unit was found to be 360 A. long and 21 A. in diameter. It is suggested that the electric eel organ acetylcholine esterase is a molecular aggregate of 30 to 50 enzymatically active units.

PAGE, Cleveland.

INCORPORATION OF GLUCOSE-U-C^{14}, GLUCOSE-1-C^{14}, AND GLUCOSE-6-C^{14} IN VITRO INTO THE PROTEIN-BOUND AMINO ACIDS OF ONE-DAY-OLD MOUSE BRAIN. H. H. SKY-PECK, H. E. PEARSON, and D. W. VISSER, J. Biol. Chem. 223:1033, 1956.

A study was made of the in vitro conversion of glucose to essential amino acids in one-day-old mouse brain. Glucose-U-C^{14} yielded radioactive carbon distributed in all of the protein-bound amino acids except threonine, while radioactivity from glucose-1-C^{14} and glucose-6-C^{14} was found in aspartic acid, serine, glutamic acid, proline, alanine, and, to a small extent, methionine, tyrosine, and phenylalanine. In the formation of $C^{14}O_2$ from glucose-1-C^{14} and glucose-6-C^{14}, the oxidative, or "shunt," pathway is not the predominant mechanism. The large incorporation of C^{14} from glucose-U-C^{14} into phenylalanine was chiefly in the α- and carboxyl carbons. Serine appears to be formed from a 3-carbon compound having its origin in glucose. Finally, carbons 1 and 6 from glucose are not incorporated into the essential amino acids. Thus glucose-U-C^{14} is found in the essential amino acids, while neither the glucose-1-C^{14} nor the glucose-6-C^{14} contributes C^{14} to the amino acids. It is concluded that carbons 1 and 6 are not precursors of essential amino acids, while one or more of the other four carbons of glucose are largely incorporated.

PAGE, Cleveland.

Neuropathology

CEREBRAL BLOOD FLOW IN POLYCYTHEMIA VERA. D. NELSON and J. F. FAZEKAS, A. M. A. Arch. Int. Med. 98:328 (Sept.) 1956.

A 48-year-old woman with polycythemia vera was studied by Schmidt-Kety cerebral blood flow techniques throughout a hospital course, punctuated by several episodes of cerebral thrombosis and terminating in death. As has previously been demonstrated in polycythemia vera, an increase in cerebrovascular resistance, with consequent decrease in cerebral blood flow, was initially noted. The cerebral metabolic rate was normal. An increase in blood flow and a decrease in resistance were noted following both carbon dioxide therapy and phlebotomy. The metabolic rate was uninfluenced prior to the occurrence of thrombotic episodes, after which it fell sharply, despite evidence of decreased vascular resistance, and consequently greater blood flow, at these times. Therapy of this dyscrasia consists of phlebotomy and maintenance therapy, such as radioactive phosphorus. The study in question suggests considerable benefit to be derived from the use of carbon dioxide inhalation. Despite the high incidence of thromboses, a hemorrhagic proclivity (poor clot retraction, tissue plethora, etc.) contraindicates the use of anticoagulants in the treatment of polycythemia vera.

PARSONS, Montrose, N. Y.

HISTOPHYSICAL STUDIES ON CORPORA AMYLACEA FROM THE HUMAN SPINAL CORD. J. R. MEYER-ARENDT, A. M. A. Arch. Path. 62:468 (Dec.) 1956.

By means of an optical schlieren method, microscopic studies were made of corpora amylacea in the spinal cord of a 53-year-old woman with diabetes mellitus and renal disease. The average refractive index was found to be 1.51, with a dry mass weight of 320×10^{-12} gm. The refractive indices for water and glycerin were, respectively, 1.333 and 1.461. Previous studies by the author had shown corpora amylacea to be composed chiefly of highly polymerized acid mucopolysaccharides and to be free of lipids, proteins, or nucleic acids.

APONTE, Philadelphia.

THE CHANGING NEUROPATHOLOGIC PICTURE OF CHRONIC ALCOHOLISM. K. T. NEUBUERGER, A. M. A. Arch. Path. 63:1 (Jan.) 1957.

Neubuerger studied the brains of 42 alcoholics, ranging in age from 30 to 70 years, one-third of whom were women. Since the material was obtained from medicolegal autopsies on patients who were in terminal state or dead when brought to the hospital, detailed clinical histories were not available. Most subjects had fatty liver with or without cirrhosis. In some there was evidence of lobar pneumonia, and in a few, of old traumatic injury to the brain. Atrophy of the brain was mild and was seen in less than 50% of the cases. The histological changes in the subjects with cortical cerebral atrophy were most marked in the middle layers, and were nonspecific and not very severe. Lesions around the mammillary bodies were seen in only two instances; slight focal demyelination of the corpus callosum, in two others.

The severest and most constant changes, occurring in 28 cases, were observed in the cerebellar cortex, and consisted of selective degeneration of the granular layer with little alteration

in the Purkinje cells. The cerebellar lesion, which was believed not to have been the result of postmortem autolysis, was diffuse, although the vermis was usually most severely involved. Histologically, the earliest changes were characterized by clumping of the granules and the presence of amorphous eosinophilic interstitial material. With progression in severity the amount of amorphous ground substance increased in amount, forming a coarsely vacuolated eosinophilic meshwork. The nuclei of the granule cells exhibited a variety of changes, including shrinking, conglutination, hyperchromatism, fragmentation, and, less often, vacuolation and liquefaction. Degeneration of climbing and mossy neurofibrils was prominent in the granular layer, whereas the baskets and dendrites of the Purkinje cells were much better preserved. Fat was absent. Glial proliferation was minimal and only occasionally seen. Changes in the olivary nuclei were not conspicuous. The pathologic changes in this group differed significantly from those in another series of cases studied by the author several years previously. Their significance and probable pathogenesis are discussed.

APONTE, Philadelphia

MORPHOLOGY OF CORTICAL CONTUSIONS. R. LINDENBERG and E. FREYTAG, A.M.A. Arch. Path. 63:23 (Jan.) 1957.

Lindenberg and Freytag report an extensive study of cortical contusions, based in part on their personal experience with 650 cases of head trauma. The pathological changes are divided into hemorrhages and necroses, which may occur concomitantly or independently of each other. The hemorrhages are usually multiple, are located at or near the crest of a convolution, possess a streak-like pattern, and are densely arranged. If superficial, they may extend into the subarachnoid space. When associated with contusion necrosis, the hemorrhage often extends into the softened tissue but usually does not invade the adjacent normal brain. If there is no concomitant necrosis, the areas of hemorrhage remain more or less confined within the limits of cortical band. In the presence of hypertensive disease they may be profuse and apoplectic. The amount of bleeding in a given case is not a good index of the duration of survival after injury. With survival of more than a few hours these foci undergo changes in color and tend to become progressively smaller. The end-result of the larger hemorrhages is the formation of smooth-walled cysts which contain few or no structural elements. Solid scars are rare with traumatic contusions, being more typical of open brain wounds. Microscopically, the focus of hemorrhage shows, in the earliest stages, a collapsed blood vessel with a shriveled wall, beyond which there are varying degrees of hemorrhagic extravasation. Solitary hemorrhages are usually due to injury to small arteries or veins, whereas multiple compact ones are as a rule the result of capillary injury. In the surrounding viable tissue the larger vessels, especially the veins, dilate. As the focus of hemorrhage enlarges, this surrounding tissue becomes gradually compressed and undergoes a series of changes, ranging from death of a few nerve cells to diffuse necrosis of all the elements with softening. Signs of resorption are seen as early as 24 to 48 hours after the accident.

Unless associated with diffuse hemorrhage, which makes its delineation sharp, the exact extent of a focus of contusion necrosis cannot be ascertained until 10 to 12 hours after trauma. At this time the necrotic cortical tissue swells and becomes gelatinous, being thus sharply demarcated from the surrounding area. During the first five to seven days it increases slightly in size, but then the edema recedes, and the necrotic tissue becomes friable and is gradually resorbed. The necrotic areas in the cortex are wedge-shaped on cross section, with the base at the crest of a convolution. The cortex around the sulci is usually spared unless the lesion is large and extends over several convolutions. In four to six months this necrotic focus becomes cystic. The degree of yellow-brown discoloration within it varies with the intensity of the hemorrhage. No scar tissue is formed within these cysts, which communicate broadly with the subarchnoid space. Microscopically, the earliest change in an area of contusion necrosis is acute shrinkage of the nerve cells. With survival for three to five hours, the necrotic areas appear paler than the adjacent tissue with Nissl stains; this demarcation is more pronounced in myelin-sheath preparations. The demarcation line indicates the final extent of damage due to trauma proper. With time, the cerebral tissue beyond this line will show a variety of necrobiotic changes, which are different from those in the area of necrosis proper and which help in estimating the age of the lesion.

In the necrotic area proper the nerve and glial cells appear pale, with small pyknotic nuclei; this is fully developed by 12 to 48 hours. The rate of cellular disintegration is often slower near areas of hemorrhage than in ischemic foci. Once the phase of necrosis is complete, it may persist unchanged for several weeks without signs of active phagocytosis.

Colliquative necrosis, so typical of ischemic softening, is not seen. Resorption of dead tissue is achieved by the cellular elements of the border zone and of the subarachnoid tissue. In the border zone, within five hours, the nerve cells become elongated and closely grouped and appear shrunken. Those closest to the necrotic focus will develop typical incrustations in their pericellular structures. The capillaries are dilated and filled with amorphous proteinaceous fluid. By the second day there is seen swelling of the nuclei of the mesodermal cells of the leptomeninges, and of the astrocytes and microglia in the border zone. With the appearance of the first gitter cells the phase of resorption begins. By the third to fourth day many of the nerve cells have disappeared and prominence of the glial tissue is apparent. There is increased formation of gitter cells; the capillaries enlarge and proliferate widely, and histiocytes from the overlying leptomeninges migrate into the necrotic zone. As the gitter cells also migrate into the focus of necrosis, the number of compound granular corpuscles increases steadily. Occasionally, proliferation of capillaries may give rise to delayed hemorrhages within the border zone. During the ensuing two months, and beginning at the periphery, the phagocytic elements disintegrate the dead tissue. At this time the lysed necrotic core is surrounded by a dense layer of ever-growing compound granular cells and by an "accessory pia-glia membrane." With survival over three months the last remnants of necrotic tissue have disappeared and the compound granular cells are inconspicuous. The resulting cyst is devoid of the vascular network so typical of cystic vascular softenings.

The authors believe that traumatic contusion necroses are the result not of anoxia but of mechanical factors. They agree with the theory previously proposed by Hallervorden that compression waves arriving and overlapping at the site contralateral to the impact area cause an irreversible gelification of the protoplasm, followed by death of tissue.

APONTE, Philadelphia.

PATHOGENESIS OF POLIOMYELITIS IN THE CHICK EMBRYO. R. LOVE and M. ROCA-GARCIA, A. M. A. Arch. Path. 63:55 (Jan.) 1957.

Chick embryos were infected with egg-adapted poliomyelitis virus by yolk-sac and intravenous routes. The development of lesions and the distribution of the virus in the embryos were studied. After intravenous inoculation the viral content of the brain rose rapidly to a maximum in 24 hours and remained high throughout; viremia increased during the first 66 hours and then subsided. After yolk-sac inoculation the viral content of the brain increased gradually, to reach a maximum in 66 hours, and then dropped slightly; with the same dose of virus the concentration in the brain at a particular time was higher when the virus was injected intravenously. Viremia following inoculation via the yolk sac increased for a short period, dropped slightly, rose again, and finally decreased slowly, the first and second peaks occurring at 24 and 66 hours.

Gross abnormalities were not seen, and myocarditis was not produced. The distribution and character of the lesions were independent of the route of inoculation, although hemorrhages were more numerous and extensive after intravenous administration. The earliest histologic changes, observed within 66 hours, occurred in the Gasserian and posterior root ganglia and in the nuclei of the sixth and seventh cranial nerves. Lesions in the nuclei of other cranial nerves followed; they were particularly prominent and severe in the trigeminal, vestibular, and cochlear, and least marked in the hypoglossal and trochlear. The spread of neuronolysis within ganglion cells did not follow a consistent pattern. Changes in the anterior horn cells were first detected 75 hours after inoculation; they were severer in the brachial, thoracic, and lumbar than in the upper cervical segments. The severity of damage to the anterior horn cells could sometimes be correlated with the degree of damage to the corresponding ganglion. After 96 hours neuronal damage was common in the substantia reticularis, pons, medulla, olivary nuclei, cerebellum, corpora quadrigemina, and optic tectum. The alterations in the thalamus, hypothalamus, hippocampus, and olfactory bulbs were less severe. Occasionally, degenerated sympathetic ganglia were seen. Ill-defined foci of degeneration were present in the forebrain, especially on its dorsolateral surface.

The authors believe that the virus reaches the central nervous system of chick embryos through the blood stream, either directly when it is injected intravenously, or following a preliminary period of proliferation in the yolk sac when the latter structure is the portal of entry. Transmission of virus along peripheral nerve pathways, they believe, is not likely.

APONTE, Philadelphia.

STUDIES ON THE DISTRIBUTION OF *N*-ACETYL-L-ASPARTIC ACID IN BRAIN. H. H. TALLMAN, J. Biol. Chem. 224:41, 1957.

N-acetyl-L-aspartic acid occurs in concentration of about 80-110 mg. per 100 gm. in cat and rat brain. It is not the source of the bound aspartic acid occurring in urine and extracts of muscle, kidney, and liver. Acetylaspartic acid is present in mammalian and avian brain and at one-fifth the level in turtle. It was not found in brains of frogs, lobsters, and horseshoe crabs. In mammals it occurs throughout the central nervous system. At birth (rat) the concentration is low and reaches the adult level in about 20 days.

PAGE, Cleveland.

GALACTOLIPIDE METABOLISM. N. S. RADIN, F. B. MARTIN, and J. R. BROWN, J. Biol. Chem. 224:499, 1957.

Mammalian brain contains several galactose-containing lipides: strandin, strandin peptide, polycerebroside, gangliosides, cerebron sulfate, and cerebrosides, as well as sulfatides. Now methods are described for isolation of galactose, as mucic acid from rat brain strandin, cerebrosides, and sulfatides. The sulfatides undergo no metabolic breakdown, but the other galactolipids undergo turnover. Evidence was found in brain for the occurrence of a protein-bound galactolipide and a rapidly metabolizable galactolipide.

PAGE, Cleveland.

FAHR'S IDIOPATHIC NONARTERIOSCLEROTIC CALCIFICATION OF INTRACEREBRAL VESSELS. A. ARENDT, Monatsschr. Psychiat. u. Neurol. 132:24 (June) 1956.

A middle-aged woman was hospitalized with the chief complaint of personality change, consisting of suspiciousness, agitation, and progressively increasing irrational behavior. Examination showed the presence of delirium and no associated physical changes. The neurological examination was not remarkable except for slight ataxia. The patient underwent a progressively downhill course, developing an intercurrent submandibular cellulitis. Consciousness became progressively more obtunded, and she died a few days after admission. Autopsy revealed cylindrical and globular noncalcific deposits in the perivascular spaces, at times impinging upon the media and adventitia. A pronounced affinity for Turnbull blue stain for iron was found. The most severely involved vessels were in the pallidum, internal capsule, putamen, and dentate nucleus. Arendt postulates that this condition is ascribable to a metabolic disturbance in the striodentate system, wherein tissue injury results in release of respiratory enzymes containing a relatively high iron content. The susceptibility of these "extrapyramidal" centers to such injury in association with a wide range of situations, including carbon monoxide and cyanide intoxication, secondary anemia, kernicterus, morphine and methyl alcohol poisoning, and Wilson's disease, is discussed.

PARSONS, Montrose, N. Y.

Psychiatry and Psychopathology

RH CHILD: DEAF OR 'APHASIC'?: 1. CLINICAL PATHOLOGIC ASPECTS OF KERNICTERIC NUCLEAR 'DEAFNESS.' V. GOODHILL, J. Speech & Hearing Disorders 21:407 (Dec.) 1956.

Studies of Rh deafness by otologists and audiologists at Children's Hospital, Los Angeles, show that Rh incompatibilities can produce not only kernicteric, cochlear, and nuclear but other icteric lesions. Damage seems to be produced by cellular anoxia, and lesions are fairly haphazard and widespread. A variety of audiometric pictures are seen: simple, stable losses of hearing; and complex types of greater degree, with involvement of the central vestibular nuclei and neural auditory pathway in thalamic and subcortical regions, with many of the characteristics of aphasia. Shifting thresholds may be the result of neurological lesions in the reticular substance. Employment of the PGSR audiometric technique shows fluctuations and erratic responses. Neurological deafness must be considered as damage not only to a simple afferent pathway but to an efferent pathway also.

PALMER, Wichita, Kan.

RH CHILD: DEAF OR 'APHASIC'?: 2. 'APHASIA' IN KERNICTERUS. P. COHEN, J. Speech & Hearing Disorders 21:411 (Dec.) 1956.

Seventy-four cases of kernicterus followed at the Cerebral Palsy Diagnostic and Treatment Center at University of California Medical Center, San Francisco, seem to show a number of aphasoid signs. Histories of these children show they are markedly jaundiced

early, are poor feeders, are quite irritable, and quickly develop opisthotonos. The child is slow in motor development, and body control is very poor, with arms moving about aimlessly. There is difficulty in visual supraversion, and frequently a delay in lateral visual movement. Dysarthria, of varying degrees, is usually present. The author speculates that perhaps some of the 80% of the kernicterus patients who have been reported as deaf or hard of hearing may be aphasoid.

PALMER, Wichita, Kan.

RH CHILD: DEAF OR 'APHASIC'?: 3. LANGUAGE AND BEHAVIOR PROBLEMS OF THE RH 'APHASIC' CHILD. H. HANNIGAN, J. Speech & Hearing Disorders 21:413 (Dec.) 1956.

Twenty aphasoid children were studied for periods ranging from 3 to 18 months at Northern California State Residence School for Cerebral Palsied Children and the outpatient clinic at Northern California Cerebral Palsy Diagnostic Center. Progress varied greatly and did not correlate directly with estimated intelligence. Of the 20 children, 12 were considered to have normal peripheral hearing. Therapy had to be designed with gestures and similar cues. Recognition and naming of pictures or objects were inconsistent. Many of these children coined their own names for things. So-called "easy" words were not necessarily easier for these children. Group words caused confusion. Words presented in play situations or while the child was engaged in an interesting activity seemed to be picked up more easily. Children receiving lipreading training do not seem to improve more in late stages than those without lipreading. Too direct attention to placement of articulators seems to result in syllabic confusion. Aphasoid children seem to respond to familiar voices better than to unfamiliar voices. Delayed responses are common even after considerable langauge is developed.

PALMER, Wichita, Kan.

News and Comment

ANNOUNCEMENTS

Association for Research in Nervous and Mental Disease.—The annual meeting of the Association for Research in Nervous and Mental Disease will be held on Dec. 13 and 14, 1957, at the Hotel Roosevelt, New York. The subject of the meeting will be "The Effect of Pharmacologic Agents on the Nervous System."

A General Theory of Treatment in Psychiatry

HAROLD A. RASHKIS, M.D., Ph.D., Philadelphia

Introduction

An empiric is defined as follows:[1] "1. a A member of an ancient sect of physicians who disregarded all theoretical study and based their knowledge and practice on experience alone. b One who deviates from the rules of science and regular practice. 2. One who follows an empirical method; one who relies upon practical experience; hence, a quack; charlatan."

On the other hand, to be eclectic means to be "selecting; choosing what is thought best in doctrines, opinions, etc., from various sources or systems. . ."

The clinical psychiatrist is accordingly in somewhat of a dilemma. He certainly wants to be free to pick and choose, from among various methods of treatment, that which seems most appropriate for each individual patient. Naturally, such choice must be based on practical experience, yet not on superstition or on sheerest expediency, for to do so implies "empiricism" in its more unfavorable sense.

To be a true "empiric" implies that one has no systematic or theoretical basis for one's practice. To be "eclectic," on the other hand, implies that one sees some good or some utility in many systems or in many theories. An eclectic psychiatrist might treat one patient with psychoanalysis, one with relationship therapy, and a third by "total push," while prescribing for a fourth chlorpromazine or electroshock. Underlying each of these methods of treatment is some theory regarding the modifiability of human behavior. Unfortunately, as matters stand at present, these theories are not interchangeable, nor is there one common theory to account for all the others. We cannot adequately account in Freudian terms for the effect of chlorpromazine, nor can the effectiveness of a therapeutic milieu yet be explained in terms of neurophysiology.

Knowing these theoretical deficiencies to exist, how is it that we are able to maintain our feelings of self-consistency despite the diversity of patients treated by a diversity of means?

First of all, in any field of practice, pluralism is not an impossible philosophic position. One of our outstanding American philosophers, William James, the leading proponent of the "functional" school of psychology,[2] and a founder of the philosophic school of pragmatism,[3] was himself a pluralist. This means that he could tolerate a universe in which all aspects or meanings were not held accountable to a single explanatory principle. We all differ, of course, in our ability to deal with diversity or to "tolerate ambiguity," [4] and while some of us can survive happily as eclectics—just as persons throughout history have survived as empirics—there are others who must seek a single explanatory theme or a definite orientation, be it "organic," "functional," or any one of a number of blends.

However, regardless of our individual diatheses for orderliness, or for its lack,

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medical science as a whole is extremely intolerant of ambiguity. The frequently heard criticism that "psychiatry is not scientific" does not mean that nothing that psychiatrists do is scientific; the problem is, rather, that psychiatrists do so many different things that seem unrelated not only to each other, but to anything being practiced in the medical community at large. Perhaps this latter alternative has contributed to the popularity of the newer drug therapies: Now psychiatrists are able to treat their patients in the way other doctors treat theirs.

But it is not the use of drugs or of other somatic means per se that will make psychiatry scientific. Provided a broad and reasonable theoretical underpinning, psychological therapies can be just as scientific as physical ones. Yet we cannot dichotomize and remain scientific; we cannot have one theory which describes psychiatric treatments of the mind and another for psychiatric treatments of the body.

It is the thesis of this paper that many of us eclectics are not pluralists at all, and that there is actually an internally consistent theory which is implicit in and which underlies our psychiatric practice. It is a further thesis that this theory is relatable to the main stream of scientific thinking. Naturally, this theory is here described in the there terms may find no general agreement, terms in which I formulate it to myself; but I hope that some will find them useful.

The Theory

1. *The Phenomenological Field.*—Although we have no direct access to it, that with which we are most concerned in psychiatry is the patient's conscious state. When his mental status examination findings are within normal limits, we agree that the patient is well. This implies, of course, that there is a good correspondence between what he says is going on around him and what we agree is actually happening, between what he says he is doing and what he actually does. When his mental status examination, as here qualified,* is normal, we say that the patient is well.

Another way of referring to the patient's conscious state is to speak of his "perceptual field" or his "phenomenological field." This subtends everything that he consciously perceives or of which he is consciously aware, all of the information † available to him in his dealings with the world. This field includes not only his memories and his perceptions of external stimulus objects and situations, but also a representation of his own body, its tonus, and its movements.[5] He has information not only about where he has been, what has happened to him, and what he has done, but also about what he is doing and what he says he is doing. Too, he has information about what is happening to him, what he thinks is going to happen, and what he thinks he is going to do.

The reason that the term "information," rather than "facts" or "knowledge," is used here is to leave the door open to the possibility that the information received by or available to the patient may be incorrect or too jumbled for him to use effectively.

On the other hand, the patient may have clear-cut information from his various sources, internal and external, past and present; but he may not be able to integrate this information in a useful way.

2. *The Organization Factor.*—There is in the brain no known structure or structural complex which directs our attention to one source of information rather than to another. The reticular formation has in recent years been implicated in consciousness and in attention,[7] and various brain areas, particularly 8s, have been thought to be involved in the performance of adversive movements, such as we make when our attention is directed in a very primitive way.[8] No particular part of the brain, however, has been at all convincingly

* It is not implied that a formal mental status examination, with or without additional psychological tests, is always done before a patient's treatment is terminated.

† This term is used here as in communication theory (cf. Shannon and Weaver[6]).

likened to a "master switch," which focuses the mind now on an external stimulus object, now on a memory, now on a pattern of kinesthetic impulses. These shifts in attention certainly do occur, and their importance in psychopathology is so obvious that it need not be here belabored. How and why these shifts occur; why attention is maintained rigidly by some patients and extremely loosely by others, and why individuals show personal variability deserve the most careful investigation.

Not only are we lacking in anything near an adequate understanding of the attention process, but we are further at a loss to account for how information from that to which we have been attending is related to information derived from other sources.

There has been postulated an "organization factor" to account for the correspondence between a person's overt behavior and the way in which he verbalizes that behavior, and it has been demonstrated how various clinical groups differ in the functioning of that factor.[9,10] It is not known where in the brain this factor might be localized; so at this stage of our knowledge it is perhaps excusable if we call upon the organization factor to perform yeoman service—which might actually turn out to do violence to the involved neural structures when and if they are identified. As long as we speak in functional rather than in structural terms, we preserve considerable latitude in the grouping of functions.

The following functions for the organization factor may now be proposed:

1. Directing or shifting the focus of attention
2. Coordinating information from various internal and external systems

There may actually be involved here two or more distinct psychological functions, but for the purpose of this exposition they will be grouped under the "organization factor."

This factor may then be characterized as a central perceptual mechanism which selects that to which we attend and which shifts our attention to a new frame of reference, set,[11] or "mazeway."[12] As it shifts our attention, there is periodically scanned an ambiguous situation or a choice-point. Accordingly, all of the relevant information must be brought to bear from our perceptual fields, past and present, including the feed-back from our various attempts at resolution. We are then in readiness for decision making and for the performance of integrated acts.

3. *The Principle of Disorganization.*—When a person becomes mentally ill, regardless of how superficially composed or well systematized his facies or productions may appear, he may be considered to be in a state of psychological disorganization. This means simply that he is no longer able to carry out for long an integrated series of socially meaningful acts.

How does this come about? There have already been described two psychological variables: the phenomenological field and the organization factor. An answer will be offered in these terms.

First of all, it is essential to acknowledge the reactive nature of mental disorder, the prototype of which exists in the acute situational reaction. All disorders may be thought of as reactive to some extent, presumably having some place in a continuum of reactiveness.

Second, each individual, patient or not, may be thought of as possessing an organization factor that is capable of a certain level or a certain range of functioning. This implies that some persons have a much more effective organization factor than do others. There is a further implication that this is a constitutional factor, with the reservation that it may be influenced by early life experiences. It is through this factor that, for example, the genetics of schizophrenia[13] might be manifested.

Psychological disorganization, then, may be thought of as arising from disorganization in the phenomenological field. This, in turn, may reflect true disorganization in the reality situation that is perceived by the patient, or it may be a function of an inadequate organization factor. This system must be conceived of as having considerable flexibilty: Psychological disorganization may

result from any of an infinite combination of reality disorganizations and defective organization factors. It should be obvious that a very effective organization factor should make the individual tolerant of a high degree of reality disorganization. On the contrary, a very weak organization factor would not protect the individual against the slightest amount of situational ambiguity.

Finally, it is proposed that essentially the same clinical picture may be produced by psychological disorganization whether it results primarily from situational factors, as reflected in the phenomenological field, or from a faulty organization factor; this would account for the resemblance between the more reactive types of schizophrenia, on the one hand, and process schizophrenia, on the other. The prognostic implications should be obvious.

4. *The Principle of Reorganization.*—Regardless of how the patient became mentally ill, it is the psychiatrist's primary job to get him well. The formulation of etiological statements or of theoretical considerations such as this have significance only as they contribute to that end. Yet we need to know why it is that some patients do well on psychotherapy or environmental manipulation, while others require somatic therapies—and still others resist all attempts at treatment.

Before creating the impression of oversimplicity, it should be acknowledged that all treatments, whether primarily psychologically or somatically oriented, have their representation in the patient's phenomenological field. This means that to one patient insulin shock may mean symbolic death[14] and help him for this reason, whereas to another patient somatic treatment may be of little or no psychological import, operating essentially through the transmission of energy to significant neural structures.[15] In still other patients the psychological and somatic aspects of electroshock may be of more or less equal significance.

Having acknowledged the amphoteric, polyvalent, or "overdetermining" nature of therapies, an attempt may be made to characterize treatment as tending toward (*a*) direct restructuring of the phenomenological field (perceptual reorganization) or (*b*) strengthening of the organization factor.

(*a*) Perceptual Reorganization: Obviously, there is no direct way in which we can reach into the mind and restructure what the individual perceives. We can teach him to attend to certain aspects of his environment by encouraging certain types of responses (reinforcement) and by discouraging others,[16] but we cannot make him see for any considerable length of time that which is not there to be seen.‡ We can, however, take steps to alter that which is there to be seen; i. e., we can manipulate the patient's environment, or we can clarify his perception of it by supplying information in addition to what he already has. Similarly, we can reshape his body image by taking steps to reduce bodily ills. Clearly, methods of modifying the external and internal environment, and hence the perceptual field, are most relevant in those cases in which there is a major reactive component.

Another way in which we can help the patient to reorganize his perceptual field is to homogenize his environment, to increase its information output (to the patient), and to reduce its noise level. We have research in progress § at Eastern Pennsylvania Psychiatric Institute to investigate the manner in which patient behavior changes as staff attitude becomes more consistent. This has been studied in a somewhat different way by Greenblatt and others.[17]

In clinical practice it is often observed that meeting with the patient's family and achieving a measure of agreement among them is frequently accompanied by the patient's taking a turn for the better. This improvement is sometimes explained in the question-begging terms of "anything you do actively tends to help the patient," or in the equally unsatisfying terms of "an act of

‡ The effects of hallucinogens are in general relatively short-lived.

§ In collaboration with Dr. A. F. C. Wallace.

love." I believe this phenomenon can more adequately be understood if it is cast in the framework of increasing the orderliness of the patient's perceptual field. As the field becomes more orderly, its components assume the status of bits of information, which are then utilizable by the patient in his decision-making activities.

In certain forms of psychotherapy, particularly of the so-called "directive" variety, and including all types in which the therapist assumes a very active role, as in direct analysis,[18] there may be a variety of interpretations as to why success should be achieved. One thing is clear: The role of the therapist is clearly formulated in the patient's perceptual field. It is not difficult to visualize how a clearly defined therapist can, if he has sufficient prestige, restructure the patient's phenomenological world pretty much as he pleases. Suggestion is involved here, of course, and the permanence of the changes induced depends on a multitude of factors.

Sometimes when we make no direct therapeutic effort, our patients seem to get well anyway. In reporting the results of a particular phase of a drug experiment during which patients received no drugs, we coined the phrase "milieu effect" to account for the improvement shown by some of the patients.[19-21] This effect was assumed to result from their having been introduced into a new milieu, involving the formation of new relationships and the receipt of information that was not only new but systematic or organized. This effect is an excellent example of the principle of perceptual reorganization.

This phenomenon, i. e., restructuring of the phenomenological field, can occur "spontaneously." In his "Varieties of Religious Experience," [22] William James has described the phenomenon of religious conversion as a refocusing of the attention, so that matters which were formerly at the periphery of consciousness now become central, thus imparting new values and a new meaning to life. Shamanism and the psychology of prophesy have been described by Wallace,[23] using the term "mazeway resynthesis," in a manner compatible with the principle of perceptual reorganization.

However, when we talk of "spontaneous" restructuring of the perceptual field, or of that which is peripheral now becoming central, we are speaking not of some mysterious or unknowable mechanism, but of the workings of the organization factor. In psychiatry, when we wait for "spontaneous" change, we may find ourselves waiting a long time. Hence I should like to consider at this time ways in which the organization factor may be modified directly.

(*b*) Treating the Organization Factor: Popularly, we sometimes speak of a person's mind as having a tendency to wander. A matter allegedly at hand may be sharply in focus for one person, while a second may be only dimly aware of it as his eyes focus on infinity, staring out into space. Some of us attend to every little ache and pain, or are preoccupied with each acousma or musca volitans. We may be prone to concentrate, preoccupied, on business, pleasure, love, or hate, or on one grand theme or another. Our consciousness may be drifting; yet when we hear the clarion call to attention, we attend.

Among our patients, however, are many whose attention we cannot gain, or whose cathexes we cannot disengage. This characteristic we term rigidity, or loss of the ability to shift, which is frequently accompanied by loss of the abstract attitude.[24] It is obvious that no matter how effectively we are able to structure the patient's environment, he will not be helped unless he is enabled to pay attention to what his life situation actually is, unless he is able to conceptualize essential relationships. He cannot receive information if his channels are closed or otherwise occupied, as is the case with dysfunction of the organization factor.

Not knowing where the organization factor is located, in a structural sense, or how best it may be approached, we use a variety

of methods, alone or in concert,[25] to effect some profound change in the functioning of the psychic apparatus. We may seek to do this subtly, as by psychoanalytic psychotherapy, or violently, as by electroshock,[26] or, less commonly today, by the cold shower.[27] Similarly, attempts have been made to reach the "master switch" surgically, topectomy, for example, having sought it in the frontal lobes,[28] thalamotomy in the thalamus.[29]

Exception may well be taken to lumping psychoanalysis with electroshock, psychosurgery, and the cold shower. This exception is justifiable, and a distinction may be clarified by considering an analogy with a broken or defective channel selector on a television set. If the selector "locks" on Channel 3 and we want to see a particular program on Channel 4, for the moment we might not be very concerned could we get Channel 4 by turning some unpredictable combination of knobs or by kicking the set. We might get Channel 4 while the indicator read some other channel; but if it were the particular program we wanted, this might not concern us excessively. On the other hand, if we wanted to have the channel selector repaired, we should certainly go about it by other, more systematic means.

Essentially, this means that some therapies, such as EST, might "unlock the master switch" by doing something or other to the organization factor, but the dysfunction in the factor would remain unless a thoroughgoing attempt were made to reorganize the factor, or the "basic personality structure" in this case, as by psychoanalysis. Of course, it is conceivable that in some cases there is nothing very wrong with the organization factor, except that it has temporarily gotten stuck, leaving the patient concentrating on a particular complex of ideas, which, though true, may not be particularly relevant to his life situation, e. g., as in an agitated depression. In this special case, "unlocking" the organization factor, as by electroshock, might be all that is needed, granted an essentially adequate underlying personality.

There emerges the proposition that most of our therapies cannot be expected to achieve a syntonic reconstruction of the organization factor. Certainly, the tranquilizers, which may be conceptualized as reducing the intensity of messages in the phenomenological field, cannot be thought of as restructuring the organization factor. On the other hand, it has been suggested that psychoanalysis might achieve a beneficial reorganization of the organization factor. This is possible to the extent that this factor is not completely constitutional, but, as earlier suggested, is influenced by early life experiences.

It is also possible that the influence of life experience on the organization factor is insignificant. In this case, of what value would be hard-won insights? Clearly, in the plausible instance of irreversible dysfunction of the organization factor the information gained through psychoanalysis could be considered only as a means for restructuring the perceptual field. We would then be (or are, as the case may be) in the position of seeking to reconstitute a factor about whose function we know little and about whose localization we know less. It seems likely that this would have to be achieved by physicochemical means, the nature of which is not only beyond the scope of this paper but beyond present knowledge.

Application of Theory

It should be apparent that this over-all approach to therapy relies heavily on the evaluation of situational factors surrounding the patient and, more especially, the manner in which they are reflected phenomenologically or, simply, how they appear to the patient. It also relies heavily on the psychological evaluation of the defect in the organization factor. In order to accomplish these evaluations, the psychiatrist must rely heavily on the social worker and the psychologist or psychophysiologist.

The extent to which these nonmedical specialists are able to make their contribution depends on the extent to which they

apply themselves to the work that their training has prepared them uniquely to do. To the extent to which they merely duplicate the work of the psychiatrist, their contribution is minimal. In many ways it is gratifying to the psychiatrist to have his formulation confirmed from other sources; but when the therapeutic team becomes a "mutual admiration society," there is a tendency to lose two independent sources of information: the situational analysis and the psychophysiological evaluation. I shall not go into detail as to how the situational analysis and the psychophysiological evaluation might best be performed. These are research matters, and we are investigating them intensively at the Eastern Pennsylvania Psychiatric Institute.

Certain principles are already apparent; this, of course, will be a tentative statement; and should it sound dogmatic, it is not so intended.

1. Unless the patient is dangerous to himself or to others and he cannot otherwise be controlled, somatic therapy, including psychopharmacotherapy, should not be used until the patient, his life situation, and his response to milieu ‖ have been adequately investigated.

2. If the patient's life situation is manipulatable, and if it seems that his disorganization has resulted primarily from circumstantial factors, there seems little point in directing the full weight of our therapeutic endeavors toward the patient. If the patient's life situation can be satisfactorily altered by working with his family, what is the rationale for prescribing (for the patient) massive doses of tranquilizers or a lengthy course of electroshock and/or insulin?

3. On the contrary, if the patient is an extremely inadequate individual, with a severe deficit in his organization factor, there is little to be gained from intensive analytic efforts with his family—except to such extent as is necessary to help them gain an understanding and acceptance of the patient's disorder. If, for example, our patient is a refractory young female catatonic, we might consider her mother schizophrenogenic and we might dislike her, but if she (the mother) is herself making an adequate adjustment, we have no license to urge her into treatment or otherwise to tamper with her life situation.

4. In many or most cases there is a combination of situational factors, on the one hand, and a deficit in the patient's organization factor, on the other. Both aspects of the case require handling. Who is to do all this work? Clearly, the psychiatrist cannot manage alone. In many cases situational analysis suggests the need not only for working with the family, which can be accomplished with the aid of a social worker, but for the advice or guidance of variously trained or experienced persons. How many of us feel equipped to give legal, economic, or religious counseling—to name only a few areas. Are we to conclude that such guidance is not our responsibility; or, if we feel that it is, how do we coordinate our professional activities with those of other counselors or therapists? How do we best coordinate somatic therapy with environmental manipulation? Some thought has been given to these matters, but they are by no means solved.

Comment

One of the requirements for a good theory is that it offer hypotheses for future research. On the other hand, I may have raised more questions than I have answered.

A theory stands or falls on the assumptions on which it is based. I have assumed a phenomenological or perceptual field and an organization factor. If the first of these does not exist, we must also do without the notion of consciousness. Without consciousness we should have no need for the concept of the unconscious, and we would lapse into behaviorism. While much of phenomenology can be better expressed in behavioral terms, there yet remains much that can be communicated most meaningfully in terms of

‖ Cf. Rashkis and Smarr.[8]

our mutual subjective experiences; the subject matter of this dissertation I would class in the latter category.

As for the organization factor: It was originally well anchored between stimulus and response. Its use in this paper has strayed from the operational terms in which it was originally defined,[9,10] but it remains a scientific contruct, accordingly subject to revision as accumulated data warrant. As suggested earlier, it may not turn out to be a simple or a single factor. At the present time it seems useful in its present state.

Finally, a theory is only one man's way of looking at things; if it offers him convenience in grouping otherwise disconnected phenomena, it is a good theory. It is a better theory if other people find it useful and attractive, for, as Whitehead put it, it is more important that a proposition be interesting than that it be true.[30]

As regards the truth of this theory, I can only say that it seems to account for the facts of clinical practice. Hypotheses stemming from it are currently under investigation. Whether or not the two factors described in this paper remain adequate to account for the clinical facts depends on how these and other investigations turn out. I do not believe that any theory of human behavior can get by on less than two factors, regardless of what they are called; in accordance with the law of parsimony, one would not posit a third factor unless the two were found to be inadequate.

Summary

There is presented a theory of treatment in psychiatry based on alterations in two factors: the phenomenological, or perceptual, field and the organization factor. The former of these includes all information, from both external and internal sources, available to the patient in his decision-making functions. The latter factor is conceived as a perceptual mechanism whose function it is to select those aspects of the perceptual field to which the patient attends, as well as to coordinate information from different sources.

Therapies are discussed in terms of their tendency to influence perceptual reorganization, either by restructuring of the perceptual field or by revising the function of the organization factor. The question is raised as to whether any of our current therapies achieve a true reorganization of the organization factor.

Certain tentative principles of treatment are offered, chiefly in regard to the withholding of somatic therapies until the patient's life situation has been explored with respect to its modifiability. Further emphasis is placed on the desirability of permitting the patient to reorganize in a therapeutic milieu before applying intensive individual psychotherapy or somatic therapies. The limitations of psychiatrists in manipulating situational factors or in supplying certain types of information are discussed.

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Serum Oxidation Tests in Schizophrenic and Normal Subjects

Copper Levels, Adrenaline and N,N-Dimethyl-p-Phenylenediamine Oxidation Rates, and Glutathione Concentration

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Our present studies have been concerned with adrenaline and N,N-dimethyl-*p*-phenylenediamine (a derived pyridopyrimidine; DPP) oxidation by serum from patients with mental illness as compared with that of serum from normal controls and patients with nonspecific illness (i. e., without psychoses) who were shown to have high globulin levels in association with a variety of disease processes. Earlier work from this laboratory has demonstrated that in a statistically significant number of instances adrenaline oxidation in vitro proceeds more rapidly in the presence of serum from acute schizophrenic patients than it does in the presence of serum from normal controls.[1,2] In addition, it has been shown that the copper-globulin, ceruloplasmin, is the enzyme in serum which catalyzes adrenaline oxidation.[3] Recently Akerfeldt[4] has reported that the in vitro oxidation of DPP occurs sooner in the presence of serum from schizophrenic patients than in the presence of serum from normal controls. In his procedure Akerfeldt has used the dihydrochloride of DPP, whereas we usually have employed the sulfate of DPP. Our experience indicates that there is no essential difference in the reactions with the different salts.

The results to be presented in this paper support the following observations:

1. The ability of serum to catalyze adrenaline oxidation in vitro is proportionately related to its ability to catalyze DPP oxidation in vitro.

2. The ability of serum to catalyze oxidation of adrenaline and DPP is also directly related to the serum copper (ceruloplasmin) level. This oxidation is increased in association with a variety of diseases in addition to schizophrenia when ceruloplasmin levels increase as, for example, in pregnant females (last trimester) and with systemic disease showing high globulin levels.

3. The difference observed in the ability of serum from the normal controls, the schizophrenic group, and the patients with nonspecific illness to catalyze oxidation of adrenaline and DPP depends upon two factors:

   A. The serum copper level (more specifically, the ceruloplasmin level)

   B. A dialyzable reducing material which is chromatographically identical with ascorbic acid

4. Oral administration of a 1 gm. dose of ascorbic acid up to 24 hours before obtaining blood samples causes a striking reduction in the rate of either adrenaline or DPP oxidation by serum of both the schizophrenic and the control group. The reduction in rate of oxidation is similar in the two groups. This last observation indicates

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that the tests involving adrenaline and DPP oxidation are to some extent a reflection of low ascorbic acid intake by the schizophrenic patients maintained on the hospital diet.

5. Supporting previously published data,[5,6] the glutathione levels are shown to be slightly lower in the schizophrenic group than in the normal (control) group.

Materials and Methods

Adenaline oxidation and glutathione levels were measured by methods previously published.[2,6]

The method for determination of serum copper is a modification of the method proposed by Peterson and Bollier.[7] Our modification, which eliminates the titration of each sample, is as follows:

Reagents: 2 N HCl; 20% trichloroacetic acid

Buffer solution, prepared as follows:

	Ml.
Saturated sodium pyrophosphate	35.7
Saturated sodium citrate	35.7
Conc. NH_4OH	80.3

The buffer solution is diluted to 1 liter with distilled, copper-free water.

Cuprizone reagent (bis-cyclohexanone oxalyldihydrazone) 0.5 gm. is dissolved in 100 ml. of 50% ethanol. Before use all glassware is acid-washed and thoroughly rinsed with copper-free water. All reagents are prepared using copper-free water.

To 2.0 ml. of serum is added 0.7 ml. of 2 N HCl and the solution mixed and allowed to stand 10 minutes. To this is added 0.8 ml. of distilled copper-free water and 0.5 ml. of 20% trichloroacetic acid, mixed, and then centrifuged for 15 minutes at 2500 rpm. Then 2.0 ml. of the supernatant fluid is transferred to a clean, dry test tube; 2.8 ml. of buffer solution and 0.2 ml. of cuprizone reagent are added, the constituents mixed, and the color allowed to develop for 20 minutes. (The maximum is almost always reached in 10 minutes and is stable for at least 2 hours.) The optical density is then determined at a wavelength of 600mμ and compared with that obtained from standard copper solutions containing equivalent quantities of 2 N HCl, 20% trichloroacetic acid, buffer solution, and cuprizone reagent.

N,N-dimethyl-*p*-phenylenediamine-sulfate (DPP), obtained from commercial sources, is purified by boiling a solution of it with activated charcoal, filtering, and precipitating the product by addition of ethyl alcohol (10 vol.). The product is then recrystallized from methyl alcohol and is obtained as a white crystalline product, melting at 191-193 C.

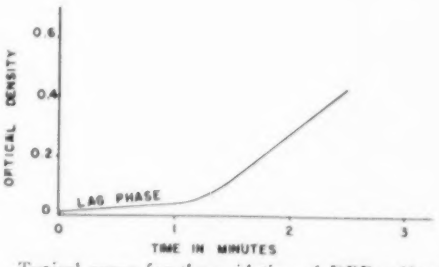
The method for measuring DPP oxidation utilizes the Beckman DK recording spectrophotometer and is as follows:

The blank cell is prepared using 1.0 ml. of serum and 2.0 ml. of 0.1 M phosphate buffer at a pH of 6.2. The sample cell is made to contain 1.0 ml. of serum, 1.0 ml. of phosphate buffer, and 1.0 ml. of DPP solution containing 2 mg. of DPP (as sulfate) per milliliter, this reagent being prepared in copper-free water in order to minimize auto-oxidation of the substrate. The sample cell is mixed by inversion and immediately positioned in the spectrophotometer. The instrument is adjusted to 100% transmission, and at exactly 20 seconds after addition of the DPP solution to the cell the recording is started, the wavelength control being set on manual and at a wavelength of 510mμ.

The reaction is allowed to proceed for 2.5 minutes (unless noted for a longer time). At the end of this period the optical density × 1000 is then used to indicate DPP oxidation. Data indicating adrenaline oxidation are also obtained by multiplying the optical density by 1000.

Results

A DPP-oxidation curve is depicted in the Figure. This curve can be seen to be made up of at least two phases: The first is the lag period, and the second is the period of active DPP oxidation. Akerfeldt[4] has pointed out that by the method which he has used for determining DPP oxidation the length of the lag period depends directly on the concentration of ascorbic acid in serum. Our observations support this view and also suggest that the slope of the curve during the phase of active oxidation of DPP is related to the serum ceruloplasmin level. The data which we have accumulated comparing the copper levels, glutathione index, DPP oxidation, and adrenaline oxi-



Typical curve for the oxidation of DPP sulfate at 510mμ. See text for explanation.

TABLE 1.—*Comparison of Average Copper Levels, Glutathione Indexes, DPP Oxidation, and Adrenaline Oxidation of Serum from Groups Tested*

Group	No. of * Subjects	Copper, γ/100 Ml	GSH Index	DPP Oxidation	Adrenaline Oxidation
Healthy controls	18	(82) 124 (150)	* 12 (54) 71 (84)	* (15) 237 (700)	* (55) 135 (390)
Nonspecifics (High globulins)	20	(112) 232 (445)	(44) 68 (105)	(40) 667 (1500)	(110) 364 (700)
Acute schizophrenics	42	(88) 147 (260)	13 (39) 69 (85)	(170) 529 (1100)	16 (25) 190 (500)
Chronic schizophrenics	85	(54) 142 (396)	11 (51) 65 (87)	16 (120) 374 (780)	16 (75) 170 (340)

* When the number of patients used for a given determination is different from the number indicated in the column "No. of Subjects," it is indicated by the number in the upper left corner of the appropriate block.

Figures in parentheses indicate range of values encountered in each measurement.

dation are summarized in Table 1. It can be seen that, although there is a rather broad overlap of values between groups, the copper levels, DPP oxidation, and adrenaline oxidation vary directly with one another, whereas the glutathione level varies inversely to these.

In order to establish definitely what factor or factors were responsible for the lag phase of DPP oxidation, we first tested the effects of dialysis of the serum against distilled water at 4 C. One volume of serum was dialyzed against four volumes of cold distilled water for a period of three hours. The serum was constantly mixed by an internal agitator. The serum volume after dialysis was measured, and a sample of the original serum, which had been stored at the same temperature during the dialysis period, was diluted an equivalent amount. The samples of serum were then warmed to 25 C (room temperature), and the DPP oxidation was determined. The data obtained by this method are presented in Table 2. In every case the amount of DPP oxidation is increased by dialysis.

The dialysates from serum samples which before dialysis had a significantly long lag phase were quick-frozen and lyophilized. The specific samples used included Patients 7 and 8 of the schizophrenic group and Subjects 2, 5, and 6 of the control group. Addition of the dried material obtained by lyophilizing the dialysates back to the dialyzed serum returned the lag phase to the DPP oxidation, although not to the same extent that was observed on the nondialyzed serum. The lessening of effect is not out of the range that one would expect as a result of the processing.

Samples of the lyophilized dialysate were triturated with 95% ethanol and centri-

TABLE 2.—*Effect of Dialysis of Serum on the in Vitro Oxidation of DPP*

	Chronic Schizophrenic Group			Healthy Control Group	
Patient	Pre	Post	Subject	Pre	Post
1	440	605	1	150	330
2	390	400	2	40	190
3	370	400	3	300	360
4	310	490	4	350	650
5	400	560	5	40	330
6	350	530	6	110	320
7	210	600	7	230	260
8	120	450	8	510	530
9	360	640	9	270	350
10	600	720	10	360	410
Average	365	539		236	376

TABLE 3.—*Effect of Orally Administered Ascorbic Acid on the in Vitro Oxidation of DPP and Adrenaline: Chronic Schizophrenic Group*

	DPP-Oxidation		Adrenaline-Oxidation	
Patient	Pre	Post	Pre	Post
1	430	185	170	15
2	710	270	240	25
3	700	70	300	40
4	460	220	185	20
5	350	50	135	20
6	305	120	..	..
7	255	60	..	..
8	315	20	..	..
9	410	80	..	..
10	780	265	..	..
Average	471	135	206	24

fuged, and the supernatant was then spotted on Whatman No. 1 filter paper for chromatographic analysis, using the descending technique with a solvent system composed of *n*-butanol, acetic acid, and water (80:10:10). The chromatograms were allowed to remain in contact with the solvent for 15 hours. They were then air-dried and finally sprayed with a solution of partially oxidized DPP. This spray produced a pink background on the chromatogram, and the presence of materials which would reduce oxidized DPP was indicated as white spots.

Pure ascorbic acid by this technique was shown to have an R_f value of 0.69. Both aqueous solutions and ethanol extracts of samples of the lyophilized dialysates revealed only one spot indicating the presence of a material which would reduce oxidized DPP. The average R_f value of this spot was 0.68, and it was indistinguishable from ascorbic acid by this method. It would appear from this that ascorbic acid is certainly the major constituent of serum responsible for the lag phase of DPP oxidation, if not the only one.

We therefore determined the effect of an orally administered 1 gm. dose of ascorbic acid on DPP oxidation and adrenaline oxidation in both a control group and a chronic schizophrenic group. Blood samples were taken just before administration of the ascorbic acid and at either 2 or 24 hours after. The data presented in Tables 3 and 4 clearly demonstrate that orally administered ascorbic acid causes a striking reduc-

TABLE 4.—*Effect of Orally Administered Ascorbic Acid on the in Vitro Oxidation of DPP and Adrenaline: Healthy Control Group*

	DPP-Oxidation		Adrenaline-Oxidation	
Subject	Pre	Post	Pre	Post
1	480	200	240	25
2	170	15	160	35
3	280	25	180	25
4	230	20	120	40
5	280	45	145	35
6	330	150	190	50
7	415	35	185	55
8	110	20	70	10
9	640	320	..	..
Average	329	93	161	34

tion in the amount of adrenaline and DPP oxidation in both the healthy control group and the chronic schizophrenic group.

Comment

The results we have obtained in these studies would indicate that possible utilization of either DPP oxidation or adrenaline oxidation for diagnostic purposes should be approached with great caution, since both appear to be affected by ascorbic acid intake. Since the dietary factors are of such great importance, it is apparent that the oxidation curves per se as a diagnostic procedure in mental illness are of little or no value. Serum copper measurements reflecting ceruloplasmin levels would seemingly be of more significance.

Akerfeldt,[4] using DPP dihydrochloride where we have used DPP sulfate, was able to obtain considerably less overlap between values for healthy controls and those for schizophrenics. However, when we have used the DPP dihydrochloride in our system, we continue to find a rather high rate of overlap between the groups. This, of course, could be due to differences in our methods of running the tests, or perhaps it may be an indication that on the average our schizophrenic group has a higher ascorbic acid intake than his and our control group a lower ascorbic acid intake.

Summary

In this study we have attempted to determine possible relationships of the levels of serum copper, N,N-dimethyl-*p*-phenylenediamine (DPP) and adrenaline oxidation rates, and blood glutathione levels in schizophrenic and control groups.

The data presented indicate that both adrenaline and DPP oxidation are influenced by two factors in both schizophrenics and healthy controls. The first factor has been previously shown to be ceruloplasmin,[3] and the second is identified as ascorbic acid.

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Jacksonism and the Works of Ribot*

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One scarcely reads Ribot any more.† His simple little books, written in a language understandable by all, are reputedly obsolete. No one denies that the founder of French scientific psychology exercised a considerable influence in his time and his last pupils, Pierre Janet and George Dumas, have rendered just homage to his memory, but the recent schools of psychopathology seem to disesteem him or to ignore him. Nevertheless, in rereading his work uninterruptedly, it has seemed to me evident that many of our most modern conceptions are contained in it explicitly. Lately various physicians and psychologists have "exhumed," from the former writings of the English neurologist Jackson, the notion of "dissolution" of the nervous and mental functions. Now, I would show here that half a century ago Ribot himself was not only an authentic Jacksonian but a veritable precursor of the present neo-Jacksonism.

I. Ribot and Jackson

It is a curious history, that of this philosopher of classical literary formation, who, on graduating from the Ecole Normale, where he had as teachers Caro and Lachelier, decided to evaluate his own education and to turn toward the study of science, after the example of Taine. In revolt against the university philosophies of his time, he criticized sharply the eclecticism of Victor Cousin and concluded that it was necessary to return to school, but this time to the school of facts, "precise, exact, indiscutable." Just as did Taine, he sought models among the English positivists, and, in his preface to the portrait of English psychology, he announced the arrival of a psychology independent of metaphysics. His purpose would be to classify, reduce, and arrange in a system the progress of the physical and natural sciences, of linguistics, and of history, "an immense mass of facts which still awaits its Kepler or its Newton." This philosopher proposed, therefore, to study psychological problems by the experimental methods of which Berthelot, Cournot, Claude Bernard, and Renan had just made fruitful application in other fields.

Now, among the experimental data, the pathological fact presents for the psychologist a very particular interest. In order that psychology may become a science, it is not sufficient to observe; one must also study the variations of the phenomenon, which represents in a way an experiment. Claude Bernard had demonstrated the interest of the pathological method in physiology and concluded that the laws of disease are not fundamentally different from those of health; the same idea inspired Ribot in the domain of psychology. "The morbid derangements of the organism which entail intellectual disorders, the anomalies, the monstrosities of pathological nature are for us experiments prepared by nature and all the more precious

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† In the United States the ignorance of French psychiatric thought is regrettable. For this reason it has seemed worth while to publish a translation of this admirable study of the work of a French philosopher, Théodule Ribot, teacher and predecessor of Pierre Janet in the chair of experimental and comparative psychology at the Collège de France. The original was published as the fourth of the "Études de psychologie médicale" by Jean Delay, in 1953.[1] It was translated and is here republished, with the consent of the publishers, by Percival Bailey.

the more rare is experimentation in this field."

Unfortunately, not being himself a physician, he had to limit himself to gathering observations made by others, but he knew how to choose them with remarkable discernment and to comprehend their significance often better than those who had reported them. As a matter of fact, those physicians are rare to whom it is possible not only to observe with sagacity and to transcribe meticulously their observations, but also to meditate on the general laws which derive from particular cases; for that there is needed an unusual combination of gifts, qualities of analysis and those of synthesis. Ribot understood this better than anyone, and, suffering because he could use only documents at second hand, he demanded of the young philosophers who followed his instruction that they study also medicine. One knows how fruitful this initiative was destined to be. However that may be, Ribot found in the works of French alienists, from Cabanis to Moreau de Tours, an ample harvest of data which he did not fail to utilize, but the guide whom he chose to conduct him through the labyrinth of psychopathology was the English neurologist Hughlings Jackson.

I have often asked myself how and why Ribot, the first in France, and almost half a century in advance, had immediately comprehended the exceptional value of the ideas of Jackson for the understanding of normal and pathological psychology.‡ Undoubtedly, one can explain it in part by a common formation, to wit, the determinative influence of the evolutionist philosophy of Herbert Spencer on Jackson, as well as on Ribot.

Hughlings Jackson was a disciple of Spencer. He set himself the task of applying the evolutionary doctrine to nervous and mental diseases, conceived as dissolutions, that is to say, as regressions of evolution. He wrote:

> The doctrine of evolution is not simply synonymous with Darwinism. . . . Herbert Spencer applies it to all sorts of phenomena. The application of this law to the nervous system is the most important for physicians. For a long time it has seemed to me that our researches on the maladies of the nervous system will be facilitated if we consider them as regressions, that is to say, as dissolutions.

As early as 1868 Jackson had demonstrated that the motor troubles engendered by a lesion of the nervous system consist of a disorganization of the most complex, the most voluntary, and the most differentiated aspects of the motor function, which is *ipso facto* reduced to its simplest, most automatic, and least differentiated aspects. In a series of articles and, in particular, in his Croonian Lectures (1884) he erected a general theory based on three fundamental principles.

Evolution follows an ascending course, which goes from the inferior nervous centers, the simplest, the most automatic, but also the best organized, toward the superior nervous centers, the most complex, the most voluntary, but also the least organized. Dissolution follows a descending course, going from the most complex, the most voluntary, and the least organized toward the simplest, the most automatic, and the best organized. In short, dissolution follows an order inverse to that of evolution; such is the first Jacksonian principle. The second opposes, to the general dissolutions, local dissolutions. In the general dissolution, the entire nervous system is under the same noxious influence, but the various nervous centers are not equally affected, for the highest centers, being the least resistant, yield first, the better-organized, middle centers resist longer, and the best-organized, inferior centers resist longest. In the local dissolution, disease of a part of the nervous system entails but a local regression of the evolution of the part diseased; so it may be unilateral or bilateral and limited to a definite system of centers and of sensory and motor pathways. As for the third principle,

‡ Jackson's own account of the applicability of his theory of dissolution to mental disease is to be found in the article entitled The Factors of Insanity.[3] (See also Selected Writings of John Hughlings Jackson.[3])

A modern application of Jackson's ideas to mental pathology is to be found in an article by Grinker.[4]

to wit, the distinction of negative and positive symptoms, Jackson formulates it in these terms:

> The symptomatology of nervous diseases has a double basis; in each case there is a positive element and a negative element. The evolution not being entirely dissolved a certain level of evolution persists. Therefore to say "undergo dissolution" is equivalent to saying in more detail be reduced to an inferior level of evolution. Expressed in more detail, the loss of the least organized, the most complex and the most voluntary, implies retention of the most organized, the least complex and the least voluntary.

One conceives, therefore, that nervous diseases are able to present, according to the depth of the lesion which engenders them, different clinical pictures representing different levels of dissolution, characterized each one by the insufficient, or negative, aspect and by the capable, or positive, aspect, which corresponds to the remaining capacities. These manifest themselves all the better because they are no longer subjected to control by the superior powers, which, as a general rule, control and inhibit them. The nervous system is actually a hierarchical integration of levels of evolution, and each of its disintegrations is manifested by the dissolution of a subordinating power (negative aspect) and the liberation of a subordinated power (positive aspect). One might say, in order to render these considerations less abstract, that *every nervous disease is a revolution; it decapitates the ruling hierarchy and substitutes anarchic forces for it of which the most evolved do not hesitate to take command and to substitute for the former order a new regime reconstituted for their profit.* The overthrow of power is followed by seizure of power by the elements oppressed, which oppress, in their turn, their subordinates. In the life of organisms, as in the life of societies, the evolutionary perspective is always that of a struggle for life.

From the moment of their publication, the works of Jackson were known in France. But their true introducer was Ribot, who attempted immediately a general application of Jacksonism to psychopathology. The originality which such an attempt represented 70 years ago is unquestionable, and it is certainly not to diminish it to attempt to explain it by the influence of him whom Ribot held to be the greatest philosopher of his time: Herbert Spencer. That Ribot had "Spencer for his favorite guide," as Taine noted, is a fact well known; and, besides his own writings, his disciples have often emphasized it.

Such was the admiration of Ribot for Spencer that it is not at all astonishing that he welcomed with enthusiasm a work as Spencerian as that of Jackson; he was in a way prepared for it. It is from this genetic perspective, comparing with the laws of normal evolution of a function those of its pathological dissolution, that he was to erect the entire psychopathological part of his work during 20 consecutive years. It began in 1881 with disorders of the memory, where there appeared for the first time in France an original application of the ideas of Jackson, and continues with disorders of personality, the psychology of attention, the psychology of sentiments (1896), the essay on the passions, the essay on the creative imagination, unconscious life and movements—an admirable series where one was able to see a veritable natural history of the human spirit.

One who did not mistake the Jacksonian character of the work of Ribot was Jackson himself. "The doctrine of evolution," he wrote as early as 1884, "wins every day new disciples." And, after having recalled the work of Laycock on the reflex activity of the brain, of Sir Charles Bell on the degrees of drunkenness, and of Baillarger on the dissolutions of language, he added: "As examples of dissolution, I wish to speak with the greatest respect of the original work of great value accomplished in this direction by Ribot."

The success of Ribot's works was considerable, and through them numerous French physicians and psychologists became acquainted, at least indirectly, with the work of Jackson. Taine saluted the essays of

Ribot as the announcement of a new psychology. Renan, who found there the premises of an embryogeny of the human spirit, of which he had himself dreamed when he composed in his youth the *Avenir de la science*, introduced this "experimental psychologist" to the Collège de France, where there was created for him a chair of experimental and comparative psychology (1888). Alfred Binet, giving in 1889 a picture of French scientific psychology, gave an exact estimate of Ribot's attempts:

> The method employed by M. Ribot in his admirable monographs consists in elucidating the normal mechanisms by an appeal to mental pathology. In his studies of pathological psychology, the point on which he has particularly insisted and which has become preeminent, is the law of mental dissolution. This law may be considered as the keystone of the edifice which he has constructed.

And Pierre Janet, disciple of Ribot and his successor in the chair of the Collège de France, has written that the psychopathological essays of his master were for a long time the "breviary of the psychologists and physicians."

Nevertheless, after Ribot, one scarcely spoke of Jackson in French psychology until recent years. After a long silence, we have witnessed a veritable flowering of Jacksonism, but it seems, in the enthusiasm of the rebirth, that one has somewhat forgotten the conditions of the birth, and it is thus that the name and the work of Ribot have scarcely been recalled on that occasion.

II. Ribot and Jacksonian Principles

The fundamental principle of Jackson, which underlies his entire work, is that of a hierarchy of nervous functions which evolution organizes in a definite order and which dissolution disorganizes in an inverse order.

Ribot wrote in his introduction to "Diseases of the Will":

> In these latter days several authors, especially abroad, have made an exposition in detail of certain parts of psychology according to the principle of evolution. It has seemed to me that there would be some profit in treating these questions in the same spirit but in another form—that of dissolution.

And he related his studies to those of Jackson in these terms:

> In 1868 Hughlings Jackson, studying certain disorders of the nervous system, first, I believe, drew attention to the fact that the most voluntary movements and faculties and the most specialized are affected first and more than the others.

This "principle of dissolution," or "reduction to a more automatic state" was proposed by him as the correlative of the doctrines of Herbert Spencer on the evolution of the nervous system. It is remarkable that when Ribot, in his studies of psychopathology, alludes to the theory of evolution, properly so-called, he cites it only with prudence. His point of view is a genetic perspective of evolution and dissolution of the human organism.

After having drawn from Jackson various examples of the disorganization of movements in paralyses—drunkenness, convulsions—demonstrating that the dissolution progresses from the complex to the simple, and the voluntary to the automatic, Ribot undertakes to apply this notion specifically to the activities of the spirit. He does not hide the fact that this application of a biological law to psychology may seem audacious, but "those who treat psychology as a natural science will not find anything here to protest." It is therefore in this Jacksonian perspective that he proceeds to analyze, one after another, the psychic functions. I shall restrict myself to two examples, one which opens the cycle concerning the dissolution of memory, the other, which closes it, concerning the dissolution of sentiments.

Ribot studies memory by showing that one cannot comprehend its nature without following the history of its evolution and dissolution. It is, he says, a process of organization at various degrees comprised between two levels: the new state; the organic registration. Its destruction follows a law which consists in a regression of the newest to the most ancient, the complex to the simple, the voluntary to the automatic, the least organized to the best organized.

Such is the law called Ribot's, but of which he himself emphasized the Jacksonian character:

> This law, however general it may be in regard to the memory, is only a particular case of a more general law—a biological law . . . . Hughlings Jackson first showed in detail that the superior, complex, special, voluntary functions of the nervous system disappear first and the inferior, simple, general, automatic functions disappear last. We have established two facts in the dissolution of memory: The new perishes before the old; the complex, before the simple. The law which we have formulated is nothing else than the psychological expression of a law of life, and pathology shows us in its turn a biological fact in memory.

In the same manner, in his "Psychology of Sentiments," Ribot, after having presented a general picture of the evolution of the affective life, paints a picture of its dissolution. This does not take place haphazardly, varying from man to man, but follows a regular course reducible to a formula which one can liken to a law.

The disappearance of sentiments, when it happens gradually and continuously by the effect of age or some slowly evolving disease, progresses from the superior to the inferior, from the complex adaptation to the simple adaptation, restricting little by little the field of the affective life. It delimits in this disintegration four phases, marked by the successive disappearance of the disinterested emotions, the altruistic, the egoaltruistic, and the purely egoistic. The work of dissolution, attacking the edifice at the summit, overturns one after another all these stages in descending to the very foundations. In this study Ribot does not take Jackson for guide, since Jackson never occupied himself with this problem; but the order of disappearance of the sentiments which he indicates corresponds in reverse to the order of their apparition which Spencer indicated and is situated in the same evolutionary perspective.

In brief, from the pathology of intelligence to that of affectivity, Ribot constantly applied the law of mental dissolution, of which he had made a law of general psychopathology verifying the first principle of Jackson.

Ribot understood perfectly the interest of the contrast which Jackson made between general and local dissolutions, but he preferred to the latter designation the term partial dissolution. He validated it by a certain reservation, in conformity with our present ideas, concerning cerebral localization understood in a narrow and static sense. Thus, apropos of *partial* memories or, "as certain authors say, *local*," he writes:

> We should accept readily this last denomination on condition that one does not forget that we are concerned here with a disseminated localization, in keeping with that hypothesis of dynamic associations of which we have so often spoken. Memory has been compared to a warehouse, where all our knowledge would be kept in the rooms. If one wishes to retain that metaphor . . . each particular memory has a squad of employees charged with a special exclusive service. One of these squads may be eliminated without the rest of the service suffering in a striking manner.

The recent experience of cerebral surgery confirms the justice of this remark.

Concerning local dissolutions, Jackson had specified that "the disease may attack principally either the sensory elements or the motor." A strict application of the Jacksonian principle to partial amnesias should result in distinguishing sensory amnesias, or agnosias, and motor amnesias, or apraxias. But in 1881 Ribot knew neither of the agnosias nor of the apraxias; he knew only of the works "of the rare physicians who had studied the psychology of aphasia," and, basing his opinions on their observations, especially those of Jackson, he had, nevertheless, sketched the study of dissolution of the sensory and motor aspects of language. And he showed that in partial dissolutions of memory, as in its general dissolutions, the destruction descends progressively from the unstable to the stable. The progress of the amnesia follows the line of least resistance, that is to say, of the least organization.

Concerning the problem of hallucinations, Ribot remarks:

> Nearly always all is limited to an alienation (in its etymological sense) of certain states of consciousness which the self does not consider as its own, which it objectifies, which it places outside

of itself, and to which it ends by attributing an existence appropriate but independent of its own. These facts show us "a beginning of dissolution of the personality." Ribot contrasts them with hallucinations without dissolution of the personality. "So long as the consensus which constitutes it has not disappeared, has not split itself in two, or has not alienated a part of itself, there is no disease, properly speaking, of the personality." The troubles are secondary and superficial. To sum it up, the first order of troubles corresponds to a general dissolution; the second, to a partial and local dissolution. "There must be," he specifies, "anatomical and physiological causes, unfortunately unknown, of which the discovery would resolve the problem." This text constitutes a remarkable anticipation of the present distinction between hallucination, a veritable delirium corresponding to a general dissolution of the personality, and hallucinosis, a partial and local phenomenon due to the irritation of sensory centers. The latter is a trouble of perception, "a fact of sensibility"; the former, a trouble of judgment, "a fact of belief."

The progress in cerebral localization, due, above all, to neurosurgery, proves how Ribot had been well advised in substituting for the distinction made by Jackson between general and local dissolutions that between general and partial dissolutions. In fact, it is today demonstrated that a general dissolution of certain psychic functions can depend upon a local mechanism. Ribot seems to have had an intuition of this concerning diseases of the will. Recalling that centers of inhibition exist in the frontal lobes for intellectual operations and that, according to Jackson, the frontal lobes "represent in relation to other centers, more complex combinations and coordinations, being thus a representation of representations," he added:

> Unfortunately, the investigations followed with so much order on cerebral localisation are above all concerned with the sensory and motor regions which, one knows, leave aside the greater part of the frontal region.

Now lesions of the prefrontal lobes or their surgical ablation determine a general dissolution of volition characterized by loss of initiative. On the other hand, Ribot wrote concerning the cerebral requisites of consciousness:

> Physiology teaches us that the production of a state of consciousness, an intermittent state, is always connected with the activity of the nervous system, particularly of the brain. If one could establish that every time certain physiological conditions exist, consciousness appears, that every time they disappear it disappears, that every time they vary it varies, this would no longer be a hypothesis but a scientific truth. We are far from this goal.

Now if one admits, as I have maintained in various studies, that consciousness, from a psychophysiological point of view, may be assimilated to the function of vigilance (to be conscious is to be vigilant; to be unconscious is to be asleep, and the degrees of consciousness are the degrees of vigilance), consciousness is found to be closely dependent on the cerebral mechanism which regulates the oscillations of wakefulness and sleep and is situated in the diencephalon. A strictly local alteration at this level engenders sleep, which is the very type of a general dissolution. Consciousness is then snuffed out, for example, under the probe of the neurosurgeon who touches this center, "like the flame of a candle blown out."

The Jacksonian distinction between negative and positive symptoms has been constantly applied by Ribot, for example, to the dissolutions of memory, consciousness, and volition.

In the general dissolution of memory, it is the disappearance of recent memories (negative symptom) which permits the reappearance in the foreground of ancient memories (positive symptom). Ribot writes: "The law of regression has permitted us to explain the extraordinary reviviscence of certain memories, like a return of the spirit backward, to the conditions of life which seemed forever gone"; and he specifies again more clearly concerning certain hypermnesias: "The hypermnesia would therefore be only the result of purely

negative conditions; it would be like a feeble voice which is able to make itself heard only when the loud-mouthed people have disappeared." Similarly, in the partial dissolution of memory which is represented by certain amnesias for symbols, it is thanks to the dissolution of rational language (negative symptom) that emotional language is released (positive symptom).

In the dissolution of consciousness, it is thanks to the disappearance of the highest levels of consciousness (negative symptom) that those states become evident which Jackson called by the name of mental automatism (positive symptom). Ribot recalls the cases of epileptic mental automatism reported by Jackson and interprets also these facts by comparing them to dreams. "The mental disorder which follows the attack seems to me very well defined by Jackson when he called it an epileptic dream." It is also from the angle of dissolution-liberation that he studies the somnambulisms characterized by the exaggeration of inferior activity which goes always hand in hand with the enfeeblement of superior activity, and he renews the comparison with the dream, assimilating the memory of secondary state to secondary state to the memory of dream to dream.

> In somnambulism the events of former attacks forgotten during the waking state return with the state of hypnotism. I have often remarked that at the moment of falling asleep, a dream of the preceding night, until then entirely forgotten, returned to my memory. Although I have never seen this fact mentioned in any work on the dream, I doubt that it is peculiar to me.

In the dissolutions of volition, it is thanks to the disappearance of voluntary activities of the spirit (negative symptom) that there are manifested automatic activities (positive symptom). Ribot defined volition as a power of coordination and arrest, of which the absence, or abulia, allows the appearance of irresistible impulsions. In other words, the abulia (negative symptom) conditions the impulsions (positive symptom). There is here a primary sketch of the theory which Janet will develop later under the name of psychasthenia.

"In the natural state," writes Ribot, "the desire tends to satisfy itself immediately; this it its law, and it is inscribed in the organism. Pathology shows us that this form of activity increases when volition weakens, persists when volition disappears." He gives numerous examples and takes as a point of comparison, in Jackson's manner, drunkenness. What is drunkenness if not a dissolution of the power of arrest and of coordination of the cerebrum, allowing the liberation of impulsions? To drunkenness he likens the states of cerebral exuberance which one observes in mania, where, in spite of the apparent exaltation of the faculties, the power to direct one's ideas is absent. So, far from representing a high level of activity, mania is in reality the triumph of cerebral automatism, left to itself and free of all restraint. Drunkenness or mania realizes, in the acute state, dissolutions of volition, of which certain forms of mental dysequilibrium give us examples in the chronic state. "One cites then," says Ribot, "degenerations. Let us take this vague word as synonymous of dissolution or regression. The idea of heredity, principle of conservation, is to transmit an organization with harmonious and convergent tendencies." Dissolution has a regressive character and entails a rupture of equilibrium in favor of one or many tendencies. But why has this particular tendency predominated? "What causes have determined the regression in a particular sense: homicide in one, suicide in another; kleptomania in one, erotomania in another?" It is then that he proposes a purely psychological explanation, which it seems important to me to emphasize. In effect, he saw that in mental automatism, whatever its form, realm of images, and impulsions, the unconscious life is projected with its instincts, its tendencies, its latent forces—in brief, "the dynamic unconscious." In this sense he was a veritable precursor of neo-Jacksonism

and, going beyond Jackson, he rejoined Freud.§

On the other hand, did Freud know the work of Ribot? In his autobiography he denies vigorously (and correctly) that he ever heard Janet's name mentioned during his stay in Paris. He did not make the same statement concerning Ribot. Nor could he very well have made it. Ribot's name was on every tongue, and his books prominently displayed in the windows of all the bookstores. The "Disorders of the Personality" was published while Freud was in Paris; the "Disorders of the Will" had been published in 1884, and the "Disorders of Memory" was in its third edition. Could Freud have read them? Knowing that he so thoroughly neglected to cite his sources as to astonish even his faithful disciple, Jones, one may suspect, but, to repeat Delay, "nothing enables us to affirm it."

Most likely this is just another example of the fact that, at certain epochs, fruitful ideas float around in the intellectual atmosphere at the disposal of anyone who wishes to cultivate them.

III. The Neo-Jacksonism of Ribot

Neo-Jacksonism is not only a resurrection of Jacksonism; it is also an evolution. It proposes in effect to make evident the primordial role which instinctive dynamism and the forces of the unconscious play in the organization and disorganization of functions—in other words, to integrate the discoveries of Bergson and of Freud into the work of Jackson. It is thus that von Monakow and Mourgue, whose book entitled "Integration and Disintegration of Function" (1928) constitutes the veritable manifesto of neo-Jacksonism, develop a neurobiological point of view, of which "two men had clearly seen the main lines: Hughlings Jackson and Bergson." For them the basis of organic and psychic life is a propulsive force, which they call the *hormé*, and which is nothing else than the *élan vital* of Bergson, a formative instinct beginning with which all the functions of the organism differentiate. "What hindered us heretofore," they write, "from attributing to instinct the primordial role which it merits is the intellectualistic point of view of classical psychology." They make much of the works of Freud on the role of the unconscious in the psychic life; but, although recognizing his merit in having seen that "instinct is the essential force which pushes us to act," they reproach him for having reduced all tendencies to the sexual instinct, at least insofar as the term libido is taken in that restricted sense. Other neo-Jacksonians, such as H. Claude and his school, especially Ey and Rouart, develop a related conception which proposes to harmonize Jackson and Freud. In every mental disease there would be an organic, or negative, component and a dynamic, or positive, component; a more profound study of the positive component would show it to be filled with affective and instructive examples of the life of the unconscious, in accordance with the profound views of Freud.

Now Ribot had already understood the primordial role of instinct, as well as that of the unconscious, and his Jacksonism was in reality a neo-Jacksonism. Let us return to the problem of impulsions. After having established that irresistible impulsions are conditioned by a process of dissolution, otherwise called a regression, Ribot asks whether the regression is oriented in a particular sense and why such or such a tendency predominated in such or such an individual. It is very evident, he says, that one cannot explain it by a local cause.

It has been maintained that every irresistible impulsion results from an excessive irritation of an *isolated* group of cerebral cells. Is there an isolated group of homicidal cells or kleptomaniac cells? It is really too simple.

After having ridiculed this anatomical and simple-minded "explanation," he turns to a "psychological genesis," in other words, to a psychogenesis.

§ It is interesting to speculate on a possible relationship between the work of Freud and that of Ribot. Delay asks in a footnote: "Could he [Ribot] have preceded him [Freud]? The "Psychology of Sentiments" was published in 1896, and Ribot does not mention Freud's name in it. He does not cite him until much later, in the preface to "Unconscious Life and Movements," which was published in 1914. In 1896 did Ribot know the work of Breuer and Freud, "Studies on Hysteria," which appeared in 1895? Nothing enables us to affirm it."

> One may admit, at least theoretically, that all of the tendencies are in each of us, actually or virtually. Ordinarily one or several predominate. . . . Now, the essential characteristic of a regression is to act in the sense of the strongest attraction or of the least resistance, which is a characteristic of reflex activity and the opposite of inhibitory volition, which acts in the sense of the weakest attraction and the strongest resistance. . . . The essential cause which orients the tendency in a determined direction is the constitution, the temperament, the character.

Thus Ribot admits that, thanks to the dissolution, the profound tendencies of character are able to exteriorize themselves in one form or another according to each person's individuality.

In his "Psychology of Sentiments," which is, in my opinion, his masterpiece, Ribot develops with rare vigor the idea of the primordiality of instinct. He himself takes this book to be "like a long revindication of the primordiality of tendencies" and specifies:

> I use this word—tendency—as synonymous of needs, appetites, instincts, inclinations, desires; it is the generic term of which the others are varieties; it has the advantage over them that it embraces at once two aspects, psychological and physiological, of the phenomenon.

In order to show clearly that he considers the tendency as the primordial fact of the human organism, and even of the personality, since he admits as evident "such an organism, such a personality," he summarizes in a phrase of Spinoza the spirit of his demonstration: "Appetite is the very essence of man, from which spring necessarily all the modifications which serve to conserve it."

Ribot opposes to the intellectualist theory of affective states a theory which he calls physiological, inspired by Spencer, which makes all affective states depend upon biological conditions and considers them as the direct and immediate expression of vegetative life. In it the sentiments are no longer a superficial manifestation, a simple efflorescence; they plunge to the utmost depth of the individual; they have their roots in needs and instincts. And it is this which he demonstrates in studying the affective function according to the Jacksonian method, according to the genetic perspective of evolution and dissolution.

He starts from the vital, organic, preconscious sensibility: "Below the conscious affective life is a region very inferior, very obscure, that of the vital or organic sensibility, which is an embryonic form of conscious sensibility and supports it." Some interpret it in a physicochemical manner; others in a psychological manner, "an obscure psyche which is endowed with attractive and impulsive tendencies." This "obscure psyche," is it not exactly the *hormé* of the neo-Jacksonians? Above the organic sensibility, and derived from it, come "the needs, that is to say, the tendencies, which are purely vital or physiological with consciousness added." Leaving the phase of needs, reducible to physiological tendencies accompanied by physiological pleasures or pains, we enter into the phase of primitive emotions: the defensive emotion, or fear; the offensive emotion, or anger; then the tender emotion (affection) and the emotions linked to the personality, to the self; finally, the sexual emotion (the last in the physiological order). At the root of each of these primitive emotions, there is a tendency, an instinct. Above these emotions, innate because determined by the organization itself, there are the sentiments more and more intellectualized—ego-altruistic, altruistic, and disinterested emotions. Now, the pathology of sentiments demonstrates that dissolution, here as always going from the superior to the inferior, despiritualizes and desocializes the affective function until it leads it back to the elementary functions, to "the trinity formed by the offensive instinct (anger), the defensive instinct (fear), and nutritive needs."

In the framework of the dissolution of affective function, Ribot studies also its arrests of development and shows that, even when the intelligence follows a normal ascent, affectivity can be arrested on the way at this or that stage. He makes this notion clear in relation to affective insta-

bility and compares the different degrees of "dissolution of character" to the arrests of development. This is what he calls "psychological infantilism," a notion constantly reiterated by Freudian psychopathology under the name of "affective retardation."

Thus, at the basis of the affective life, Ribot places the tendency, otherwise called instinct. Pleasure and pain are only effects which must guide us in the search and determination of hidden causes in the region of the instincts. If a contrary opinion has prevailed, it is the result of an illusion which consists of the belief that "the conscious portion of an event is its principal portion." But it is in the unconscious that the secret of affective states must be sought. Consciousness gives up only a part of their secrets; it can never reveal them completely; one must descend below them. Undoubtedly, it is annoying to have to invoke an unconscious activity, to make an obscure, badly determined factor intervene; but to wish to reduce affective states to clear, sharp ideas and to imagine that, by this procedure, one can fix them, is completely to misunderstand their nature and condemn oneself at once to a checkmate.

What sort of idea does Ribot have, then, of the unconscious, which he calls the dynamic unconscious and considers as an accumulator of energy? He distinguishes three layers, an ancestral or hereditary unconscious, which we call today the collective unconscious of Jung; a "personal unconscious coming from coenesthesia," which we call today the organic unconscious, and a "personal unconscious, residue of affective states connected with our previous perceptions and events of our life," which corresponds essentially to the unconscious of Freud. "This emotional residue, although it remains latent, nevertheless acts and can be found by analysis." It is surprising to find from the pen of Ribot texts which could be attributed today to the psychoanalysts. Let one read, for example, what he writes of the transfer of sentiments, by resemblance or by analogy.

It is in the psychological fact of transfer by resemblance which is the secret of the sentiment of love, of tenderness, of antipathy, of respect, which one feels for a person, at first sight, without apparent reason, and which is attributed to instinct. The explanation of many such cases is in the unconscious state, which is not easily grasped, but which, if it becomes conscious (the will aids in this only very indirectly) clarifies everything. There are also fears called instinctive, without conscious motives, that a little more penetrating observation can relate to the same explanation.

Concerning phobias, disgusts, sexual deviations, he gives psychoanalytical explanations before the term was created. "Some phobias," he writes, "have their cause in the events of our first infancy, incrusted in the constitution of the individual, origin of a repulsive tendency which acts as if it were natural," or, again, "the disgust is not a capricious, aimless phenomenon; it has its root in the unconscious depths of our organization." As for the sexual deviations and their "unconscious and therefore involuntary causes," he seeks their explanation in infancy. "Observations seem to show that about the age of 5 or 6 years there occur unconscious genital impulses provoking associations of ideas which serve frequently later as the substratum of our sentiments and our volitions. Most of these associations are unstable and remain in the unconscious." And he admits that "the existence of an unconscious subpersonality influencing the conscious personality manifests itself here, more than anywhere else, with an undeniable clearness."

As one follows the progression of the works of Ribot on the dissolution of the human spirit, one sees him admit little by little two great varieties of genesis. In the first variety the cause of the dissolution is an organic alteration of the nervous centers. This entails at the same time a negative component, or deficit, which betrays the lesion of a cerebral mechanism, and a positive component, or capacity, which betrays the liberation of the underlying dynamisms. Thus, drunkenness is due to a cerebral impregnation by a toxin, but one observes at the same time the dissolution of superior activities and the liberation of the charged impulsions of the instinctive tendencies of the personality. In the second variety, and in particular in certain affective dissolutions,

Ribot admits that the regression may be due to purely psychological and unconscious causes. For example, a sexual deviation may have as cause "events of infancy which one does not remember." The trouble is then purely dynamic, bound to old emotional conflicts which have compromised the equilibrium of the instinctive and affective forces: He recognizes a psychological genesis, or, as the psychoanalysts say, a psychogenesis. It is one of the merits of Ribot to have seen that "the law of regression is of general validity in biology, and probably also in psychology," and that the affective dissolution is not necessarily dependent on the intellectual dissolution.

If it is true that certain parts of the work of Ribot have been weakened by the progress of cerebral physiology, most of his ideas appear as surprising anticipations of present conceptions. The first in France, Ribot understood the importance of Jackson's theories on the hierarchy of nervous functions, the laws of their evolution and their dissolution, and he made fruitful application of them to normal and pathological psychology. Moreover, he presented evidence of the role of instincts and that of the unconscious in organization and disorganization, preceding thus neo-Jacksonism. Finally, in his studies of the psychology of sentiments, he identified affective dissolution with arrests of evolution or of regression toward infantile stages of development, hypotheses largely developed by Freud. In reading Ribot again, one realizes that many of his ideas, forgotten or ignored, have been recently rediscovered and taken for novelties. Undoubtedly, this veritable philosopher would not be astonished by this—*multa renascentur*.

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Relation of Electroencephalographic Delta Activity to Behavioral Response in Electroshock

Quantitative Serial Studies

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Recent theories of electroshock therapy [1-3] have emphasized the role of neurophysiologic changes as the basis for the therapeutic action of electroshock. Consistent with these theories, we have observed a relation between changes in certain measures of brain function and behavioral response. We have noted that evaluations of clinical improvement following electroshock are related to changes in orientation and confabulation after intravenous amobarbital,[4] learning and recall,[5] and syntactical aspects of language.[6]

In view of these observations, it could be expected that electroencephalographic studies would show a similar relationship. Numerous observers have reported consistent changes in the electroencephalogram after electrically induced convulsions. There is diffuse slowing with increased voltage and dysrhythmic activity.[7-12] Fast activity decreases, both in voltage and in percent time,[13] and in patients who are intensively treated there is a slowing of persistent alpha frequencies.[14] The degree, duration, and extent of delta activity are directly related to the frequency and number of grand mal convulsions.[8,14] Such activity is usually symmetric and appears maximal in anterior leads, and the electroencephalographic effects usually disappear in the four to eight weeks following the last treatment.[8,9]

In contrast to the consistency of these observations, studies of the relationship between the electroencephalographic and the clinical changes show conflicting results. Chusid and Pacella,[15] after an extensive review of the literature, concluded that the number of treatments rather than the degree of induced delta activity, was the primary factor related to a favorable therapeutic response. On the other hand, Hoagland et al.[16] reported a relation between changes in the percent time fast activity (more than 13 cps) and independent clinical ratings of behavioral change. Roth[2] similarly reported a relationship between changes in the clinical state and alterations in the delta response induced by intravenous thiopental sodium.

The divergent observations reflect variations in methodology. The present study is an attempt to apply quantitative methods of analysis of serial electroencephalographic records to this problem. The purpose of this study is to determine (1) the relation of changes in electroencephalographic delta activity to the behavioral response in electroshock, and (2) if a relationship does exist, the significance it may have for an understanding of the electroshock process.

Subjects and Method

1. In the initial series, 24 consecutive patients referred for electroshock were studied. Electroencephalograms were obtained prior to treatment and at weekly intervals during and after treatment, using an eight-channel Medcraft electroencephalograph and needle electrodes. Recording was bipolar, and hyperventilation activation was utilized

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during each recording. During the treatment period, records were taken on the day following a treatment, generally 25 to 31 hours later.

Grand mal electroshock therapy was administered by staff psychiatrists, using a Reiter C-47 electrostimulator. Treatment schedules were three times a week, and the number of treatments varied from 9 to 33. As patients showed a clinical response, the psychiatrist tended to give fewer and more widely spaced treatments. There were 15 women and 9 men in the series, and the ages ranged from 24 to 68, with a median of 47 years.

Evaluation of EEG Records.—A total of 160 records were obtained on these subjects. Following the suggestion of Strauss,[17] the delta index was determined for three lead combinations (frontal-parietal, anterior temporal-vertex, and parietal-ear lobe) for 60 seconds of recording for each lead. The delta index is defined as the percent time occupied by waves of 7 cps or slower.

The run of each selected lead combination was scanned, and 180 cm. (60 seconds) of recording that was artifact-free was noted. An additive map measure was run along the base of all waves of 7 cps or slower, determining the number of centimeters occupied by such slow activity. The ratio of this figure to 180 was the delta index of that combination.

After these measurements were made, the record was scanned for the slowest frequency clearly identified at least twice in these selected lead combinations, and for the highest voltage of these slow waves. The total record was also scanned for burst activity. The duration of burst activity, the regularity (modulation) of the waves in the burst, and average voltage were noted.

In the final estimates of degree of delta activity, the average delta index for the three lead combinations, the highest delta index in any one lead, the slowest frequency, highest delta voltage, and duration of longest period of burst activity were listed for each record. The 160 records were arranged in sequence for each index and the percentile rank determined. The ranks were added and the records then arranged in rank order according to this score. On the basis that the higher score reflected a greater degree of delta activity, the upper third of the records was classified as "high-degree delta"; the middle third, as "moderate-degree delta," and the lowest third, as "low-degree delta." An example of each is shown in Figures 1, 2, and 3, respectively.

High-degree delta records were characterized by an average delta index of at least 18%, a delta index of 21% or more in one of the three measured leads, a slowest frequency of less than 3½ cps, a highest delta voltage of more than 100μv, and a burst duration of at least two and a half seconds.

Low-degree delta records were characterized by an average delta index of less than 2%, a highest delta index in one lead of 3% or less, frequencies no slower than 5½ cps, voltages of less than 60μv, and burst duration of less than one-half second.

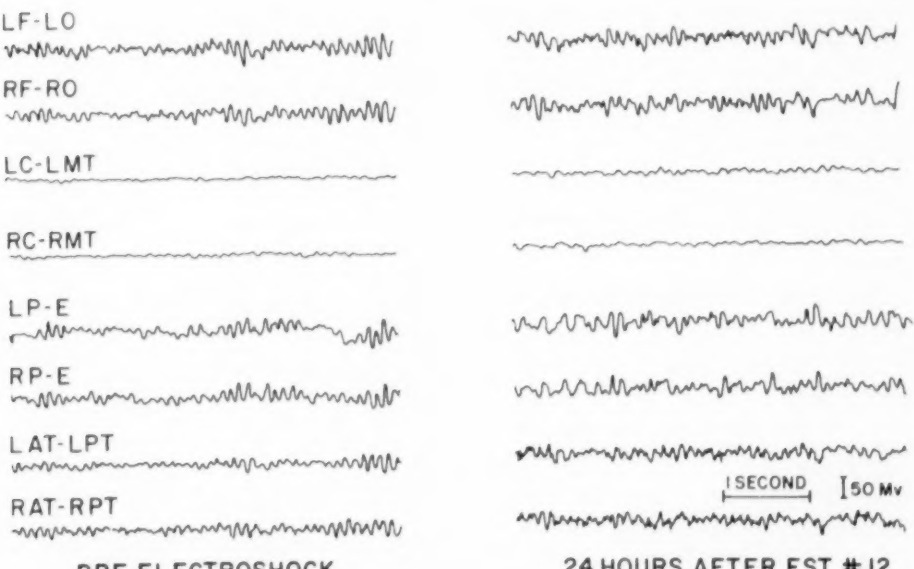

Fig. 1.—Low-degree delta activity.

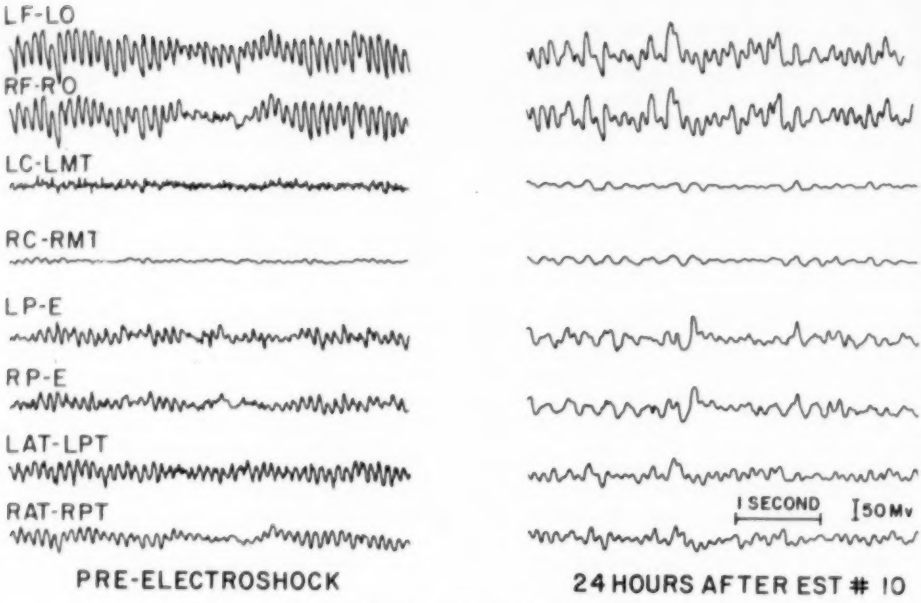

Fig. 2.—Moderate-degree delta activity.

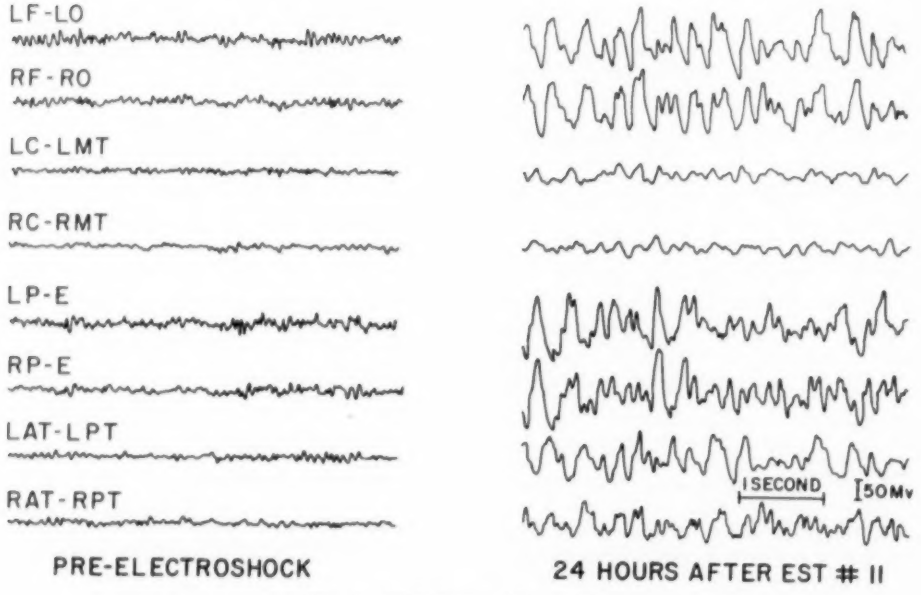

Fig. 3.—High-degree delta activity.

Moderate-degree delta records were between these two groups, with an average delta index between 2% and 18%, a highest delta index in one lead of 3% to 20%, a slowest frequency of 4-5 cps, highest amplitude of between 60μv and 90μv, and burst duration of one-half to two seconds.

2. In a second series, of 54 consecutive, unselected electroshock patients, electroencephalographic records were obtained prior to treatment, during the second and third weeks of treatment, and two weeks after treatment.

These records were analyzed using measures identical with those in the initial series. Using the original cut-off points, these records were classified as high-, moderate-, and low-degree-delta records, and the initial observations were tested in a predictive study of therapeutic response.

Evaluation of Clinical Response.—All patients were observed for at least eight weeks after termination of therapy. The patient's response to electroshock was determined on the basis of the resident psychiatrist's impression, the staff opinion, the nurse's notes, and the clinical evaluation of the supervisor in charge of electroshock. The patients were divided into three groups—much improved, moderately improved, and unimproved—according to the following criteria:

A. Much Improved: The 11 cases in this group were regarded as showing recovery or marked improvement. These patients no longer presented the symptoms which brought them into the hospital; their doctors felt they were better, and the nurses' notes confirmed such aspects as being able to sleep without medication, better appetite, and improved capacity to get along with others and participate in hospital activities.

B. Moderately Improved: The six patients in this group showed some improvement but continued to manifest symptoms of mental illness. These patients typically showed symptomatic relief; i. e., acute depressive features might be gone, but the dramatic change, so evident in the first group, was not apparent. Each patient continued to show some noticeable disturbance, such as obsessional thinking, paranoid ideas, or somatic preoccupation.

C. Minimally or Unimproved: In this group were placed seven patients in whom change was not clearly noticeable, who showed equivocal or transient changes, or who became worse. They showed fluctuations in behavior, at times appearing less ill. The changes were not sustained, however, so that by the end of treatment they appeared much as before.

Results

1. *Degree of EEG Delta Activity and Clinical Ratings.*—The initial analyses of the relation between the degree of induced delta activity and clinical ratings demonstrated a significant relationship between the early appearance of high-degree delta activity and the "much-improved" clinical ratings. Of the records in patients who were rated as much improved, 80% were classified as high-degree delta in the second week, 91% in the third week, and 88% in the fourth week of treatment. Of the records in patients who were rated as unimproved, none showed high-degree delta in the second or third weeks of treatment, and only 20% were classified as high-degree delta in the fourth week. The data are expressed in Table 1 and graphically in Figure 4.

TABLE 1.—*Electroencephalographic Percentage of High-Degree Delta Records*

	Treatment Period			
	1-3	4-6	7-9	10-12
Much improved (11)	25	80	91	88
Moderately improved (6)	0	16	50	40
Unimproved (7)	0	0	0	20

2. *Delta Indices and Clinical Ratings.*—An analysis of the relation between each of the five indices used in the final estimate of the degree of delta activity and the clinical ratings also show significant correlations. In Figure 5*A* to *E*, each index is related to the number of convulsive treatments and the eventual therapeutic evaluation. The curves

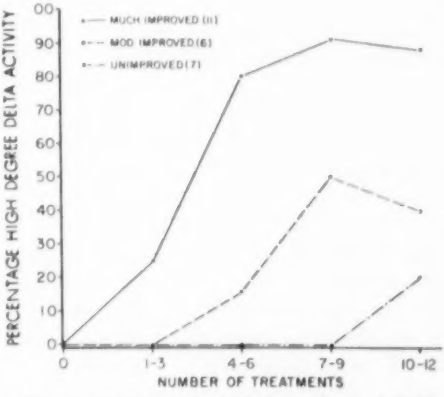

Fig. 4.—Relation of clinical ratings to development of high-degree delta activity.

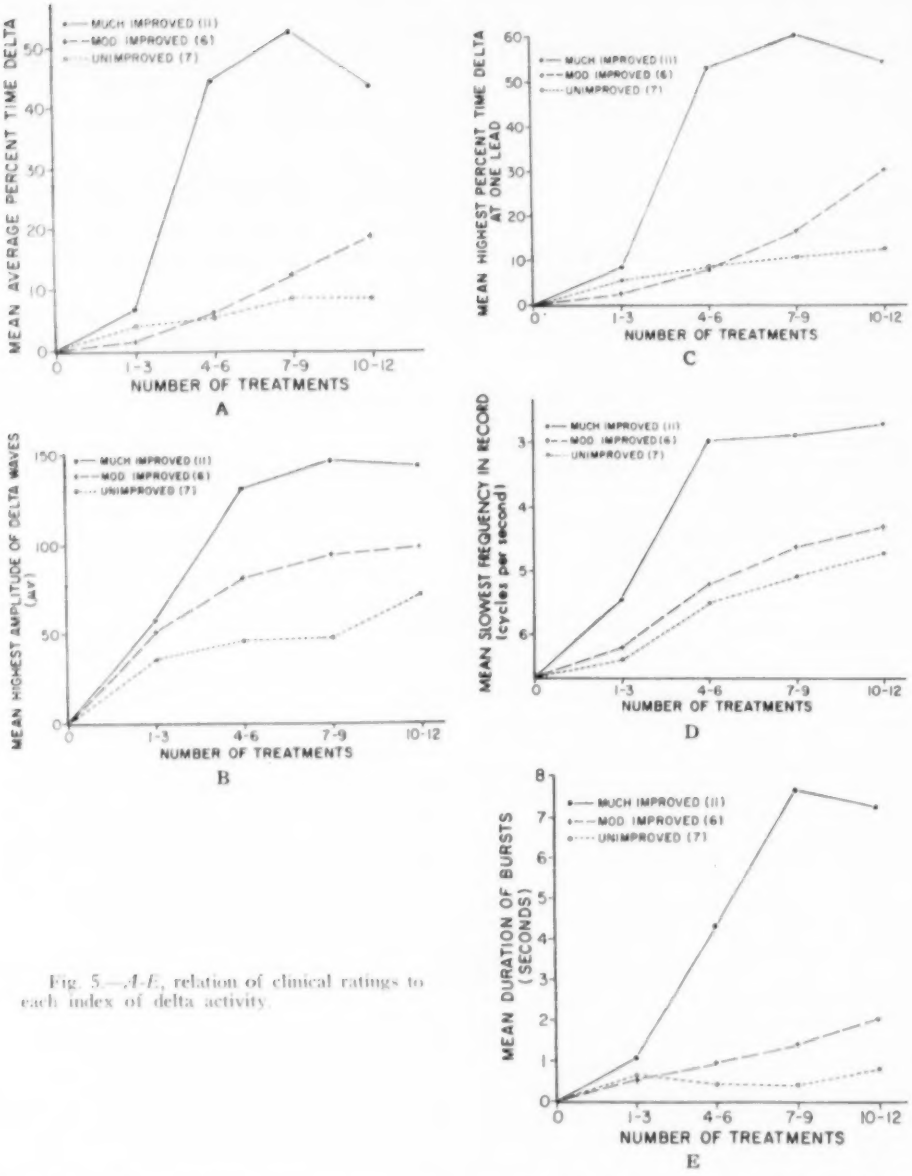

Fig. 5.—*A-E*, relation of clinical ratings to each index of delta activity.

for the highest-amplitude delta activity (Fig. 5*C*) and the slowest frequency (Fig. 5*D*) are most similar to the curves for the degree of delta activity (Fig. 4).

The other three indices (Fig. 5*A*, *B*, *C*) clearly differentiate the much improved group from the patients with the other two ratings, but fail clearly to distinguish the moderate and unimproved groups. With increasing treatment, however, the separation of classes becomes clearer.

Each index of delta activity, therefore, demonstrates a relation to the eventual short-term clinical rating which is much like that

TABLE 2.—*Intercorrelations of Individual Indices and Degree of Delta Activity*

	Average Delta	Highest Delta in One Lead	Lowest Frequency	Highest Amplitude	Longest Duration Bursts	Degree of Delta Activity
Average delta		+0.98	−0.79	+0.72	+0.67	+0.80
Highest delta in one lead	+0.98		−0.67	+0.72	+0.68	+0.84
Lowest frequency	−0.79	−0.67		−0.78	−0.47	−0.90
Highest amplitude	+0.72	+0.72	−0.78		+0.57	+0.88
Longest duration bursts	+0.67	+0.68	−0.47	+0.57		+0.63
Degree of delta activity	+0.80	+0.84	−0.90	+0.88	+0.63	

demonstrated for the combined index of degree of delta activity.

The intercorrelations of each of these indices are shown in Table 2. All correlations are significant at better than the 1% level of confidence, although the highest correlations with the degree of delta activity are noted for the frequency and amplitude measures. The lowest correlations are noted for the duration of burst activity. These observations indicate that in future studies or in clinical application frequency response and amplitude changes may serve as criteria for the degree of induced delta activity.

3. EEG Delta Activity as Index of Clinical Outcome.—Following these observations, a study was undertaken to determine whether the degree of delta response was predictive of the short-term therapeutic outcome. On the basis of the observation that the much improved patients had developed high-degree delta activity early and had sustained such activity, electroencephalograms were obtained during the second and third weeks of treatment on 54 consecutive electroshock patients.

The records were scored as to whether high-degree delta activity was achieved during both, one, or neither of the four-six and seven-nine treatment periods, and the data were related to the clinical evaluations (Table 3).

Of the patients who manifested high-degree delta activity during the second and third weeks of treatment, 67% were rated as much improved, while only 30% of patients without high-degree delta activity were so rated. Thus, the early induction and persistence of high-degree delta activity are seen to be related to the short-term clinical evaluation.

Comment

The present study demonstrates a consistent relationship between the degree and duration of induced electroencephalographic delta activity and clinical evaluation of behavioral change. While it is conceivable that the difference between our results and previous reports may be due to a variation in population, it is more likely that methodological aspects are important factors. Serial records were obtained during the course of therapy, so that the sequence of electroencephalographic change was evident. The records were obtained at a constant time interval following a treatment. Finally, quantitative analyses of the records were made instead of relying on clinical impressions. Of other investigators of this problem, both

TABLE 3.—*Patients with High-Delta Activity During Second and Third Weeks of Treatment* *

	Clinical Rating		
EEG Delta	Much Improved	Moderately Improved	Unimproved
Both high (18)	12 (67%)	4 (22%)	2 (11%)
One high (16)	4 (25%)	8 (50%)	4 (25%)
None high (20)	6 (30%)	7 (35%)	7 (35%)

* Significant at the 2% level of confidence.

Roth [2] and Hoagland et al.,[16] who carried out systematic EEG analyses, were also able to demonstrate a relationship between EEG variables and behavioral changes.

Two aspects of these observations warrant further elaboration: the relation and role of the induced neurophysiologic change to the behavioral response, and the significance of these observations for a theory of the mode of action of electroshock therapy.

1. *Relation of Neurophysiologic Change to Behavior.*—Behavioral change is a consistent accompaniment of alteration in cerebral function. Changes in mood, language, attitude, judgment, thought process, perception, and insight attend changes in cerebral function, from whatever cause, and have been extensively documented in the neurologic literature.

In this study, electroshock has been shown consistently to alter the electroencephalogram in a fashion which we have come to associate with states of altered cerebral function. The studies of Davis and Davis,[18] Ostow and Strauss,[19] Ostow and Ostow,[20] and Jung [21] have affirmed the significance of diffuse delta activity as an index of altered brain function. Symmetric, dysrhythmic delta activity has been interpreted as evidence of dysfunction of midline hypothalamic centers—the centrencephalic system.[19] Such activity is also indicative of an alteration in the state of consciousness, more marked alteration being directly related to the duration, amplitude, and frequency of the slow-wave activity.[18,21,22] The demonstrated relationship between induced delta activity and behavioral response after electroshock, therefore, permits the conclusion that changes in the centrencephalic system with attendant alteration in consciousness are the physiologic basis of the electroshock process.* A similar conclusion was presented by Roth [23] on the basis of his studies of the effect of thiopental on electroencephalographic delta activity.

Another example of the relation of the electroencephalographic delta activity to behavior is seen in reports of epileptic patients. Landolt [28,29] describes a young epileptic who was ordinarily pleasant, friendly, and cooperative for his clinic visits. At these times, records were consistently dsyrhythmic. On one occasion he was surly, irritable, and withdrawn, and his EEG was without delta activity. On the subsequent visit, the EEG was again dysrhythmic, and a behavioral "improvement" was noted. Similar observations have been reported by Brockman et al.[30] and Fabing.[31]

In a previous study [4] we had applied the amobarbital test for brain disease [32] in a serial fashion to this group of patients and reported a relationship between changes in this index of cerebral function and behavioral change. Were other tests of cerebral function to be applied in a similar fashion, it is anticipated that these, too, would demonstrate consistent changes during treatment and a relation to behavioral response, within the limits of the sensitivity of the test to reflect changes in cerebral function. In this context, electroshock may be said to be a method of inducing a state of altered brain function for extended periods, in order to achieve changes in behavior.

From this point of view, the development of a significant degree of electroencephalographic delta activity may be a readily determined guide in the rational management of electroshock therapy. In these studies we have examined various delta indices and/or the intercorrelations and have noted that the amplitude and the frequency of the induced slow waves are the best guide to the degree of delta activity. In patients in whom the behavioral response to electroshock is inconsistent with the therapeutic expectation, examination of the electroencephalogram may provide a criterion for clarification. If the induced slow-wave activity is faster than 4 cps and lower than 100 μv in anterior temporal-ear lobe or anterior temporal-frontal lead combinations, then there is

* The biochemical substrate of this process has received limited study. Emphasis has been placed on acetylcholine-cholinesterase change,[24,25] alteration in blood-brain barrier,[8] and changes in ionic and protein equilibria [26,27] by different investigators, without definitive conclusions.

presumptive evidence of inadequate electroshock therapy. When frequencies less than 3½ cps and voltages higher than 100μv are maintained for a number of weeks, the assumption may be made that an adequate degree of altered brain function had been induced and that other factors (environmental, personality, pathophysiologic) were operating to preclude a favorable behavioral response to electroshock. A similar application can be made for amobarbital tests [4] or syntactic language after intravenous amobarbital.[6]

2. Theory of Electroshock Action.—These studies of the electroshock process have demonstrated that alteration in brain function is induced early and is sustained in patients in whom the greatest degree of behavioral change is noted. We have emphasized high-degree EEG delta activity and positive amobarbital tests as indices of altered cerebral function, with the knowledge that other indices of altered brain function, applied in the same serial fashion, may also show significant alterations and a relation to behavioral change.

We have been impressed that the ratings of improvement are value judgments of the behavioral response. All patients in whom cerebral changes are induced by electroshock manifest changes in behavior. The range of behavioral patterns induced under these conditions is wide. Only certain patterns are evaluated as improved, however, while others are regarded as "unimproved." "Improvement" is a special case of behavioral response, being a subjective evaluation on the part of the observer that the patient is "better." Electroshock does not induce "improvement"; it induces a milieu of cerebral activity in which behavior is different than before electroshock. To the extent that the induced behavior in depressed patients is perceived as less complaining, depressed, agitated, or anxious, or in schizophrenic patients as less delusional, hallucinatory, or excited, the patient is evaluated as "improved." When behavior, however, is perceived as anxious, agitated, paranoid, complaining, or withdrawn, it is evaluated as "unimproved." The particular type of behavioral pattern induced by electroshock is dependent on a number of factors, such as personality.[33]

Another aspect of the rating of improvement is the environmental response to the induced behavior. The modification of mutism, withdrawal, and negativism to excitement, overactivity, and irritability may be considered a positive movement by the therapist but a disorganization by the ward physician or family. The goals of the therapist and the family, and their expectations and tolerances, are significant factors in the behavioral response of the patient to therapy, and, also, in the ratings of improvement.

These same factors are significant in the duration of the electroshock effect. The induced change in cerebral function persists for only two to eight weeks following even intensive courses of therapy. In many cases, the behavioral response is limited to this period of altered brain physiology. When induced changes in behavior are not adaptive in the milieu of the patient, the behavior reverts to pretreatment patterns. In other instances, the induced behavior is adaptive to the environment, and, we assume, sustained thereafter not by the initial change in brain function but by the newly developed interaction of the subject with environment. That this is indeed true is seen by the frequent successful adaptation of the patient to the hospital milieu after electroshock, only to have a recurrence of symptoms when discharge planning is discussed or discharge is consummated. Altered brain function provides the physiologic milieu in which there is an altered interaction with the environment—the doctor, family, or society.

These observations lead to the conclusion that electroshock therapy is a nonspecific induction of persistent states of altered cerebral function. Such altered cerebral function provides the physiologic milieu for an alteration of the organism's adaptive interpersonal behavior. Changes are induced in perception, language, mood, recall, and judgment which constitute a mode of

interaction with the environment. The type of behavior induced under these conditions is dependent upon the personality of the subject, the environment in which the interaction occurs, and the duration of the state of altered cerebral function.

A similar view of the electroshock process was initially expressed by Weinstein, Linn, and Kahn,[1] who emphasized the interrelationship of neurophysiologic changes and behavioral response. This description of the electroshock process is also consistent with the observations of Ulett et al.,[3,4] Roth,[2] and Aird et al.[3]

The neurophysiologic-adaptive interpretation of electroshock provides an operational definition of the process, which has promise of further elaboration and observation. Such a hypothesis also has application to an understanding of therapeutic process in insulin coma therapy, lobotomy, and tranquilizing agents.

Summary and Conclusions

Serial electroencephalograms obtained at weekly intervals in 24 consecutive patients referred for electroshock were quantitatively analyzed for the degree of delta activity.

A significant relationship was found between the degree and duration of induced delta activity and the clinical evaluation of behavioral change. The results were confirmed in a predictive study in an additional 54 patients.

Differences between these results and those obtained by others are explained in terms of differences in methodology.

A neurophysiologic-adaptive interpretation of the electroshock process is presented. It is concluded that electroshock is the nonspecific induction of persistent states of altered cerebral function, providing the physiologic milieu in which changes in adaptive interpersonal behavior occur.

Improvement after electroshock is seen as a special case of behavioral response under these conditions. The rating is an evaluation by an observer depending on numerous factors, including the type of adaptation, the goal and expectation of the observer (therapist, family, or administrator), and the setting in which the behavior occurs.

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Hillside Hospital.

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Persistent Effect of Chlorpromazine on Extinction of an Avoidance Response

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Clinical experience with the ataractic agents has established their value in the reduction of manifest anxiety and the consequent management of the agitated patient. The role of these agents in the production of permanent therapeutic effects is still to be established. The present experimental study suggests that the ataractic agents may be of value in the production of such therapeutic responses when utilized as adjuncts to psychotherapeutic procedures.

During the course of experimental studies of the behavioral effects of tranquilizing agents, it was observed that the injection of chlorpromazine [2] in the amount of 1.25 mg. per kilogram of body weight almost completely suppressed avoidance conditioned responses in the rat for a period of several hours. When the animals were retested 24 hours after the administration of the agent, the avoidance behavior was fully recovered. Even when the drug was administered on two or three occasions during extinction testing, the avoidance response was restored on subsequent nondrug days provided that the occasions of administration of chlorpromazine were separated by several days during which the agent was not injected. When, however, chlorpromazine was administered for three or more consecutive days while extinction trials were being conducted, the avoidance response was extinguished and did not recover when chlorpromazine treatment was stopped. Thus the action of the drug appeared to be transitory and reversible when administration was for single treatments, but when administration was continued for several consecutive days, the effects continued for the duration of the experimental extinction period.

This phenomenon would be readily understandable if it were found that a consecutive treatment schedule permitted an accumulation of the drug in the organism. Such an accumulation would be expected to persist after cessation of treatment either as a simple drug effect or, perhaps, as a toxic reaction. If, on the other hand, accumulation of the agent were not found to be an important factor, the persistence of extinction of the conditioned avoidance response would suggest that relearning had occurred while the animal was under the influence of the drug and this relearning, persisting to the untreated tests, resulted in continued extinction behavior.

The present experiment was designed to determine behaviorally whether the continuing extinction effect noted after several consecutive administrations of chlorpromazine was attributable to accumulative effects of the drug or to relearning in the conditioning situation.

Method

Sixty-two male Carworth rats were used in this experiment. The animals were 100 to 120 days old at the beginning of the experiment.

Conditioning and extinction trials were conducted in a two-compartment apparatus. The top

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Smith, Kline & French Laboratories furnished generous supplies of Thorazine.

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and both ends of the box were painted white. The back side of the apparatus was constructed of a sheet of milk glass, while the front side was a one-way vision screen. The apparatus was illuminated by two 25-watt bulbs located behind the milk-glass wall. The floor was a grid of ⅛ in. stainless-steel bars mounted ½ in. apart. In the center of the box was a 2 in. barrier constructed of stainless-steel rods which separated the apparatus into two equal compartments. An Agastat time-delay relay automatically presented the shock UCS (110 volts with 85,000 ohms in series with the animals) five seconds after onset of the buzzer CS. A more detailed description of the conditioning apparatus has been reported previously.[4]

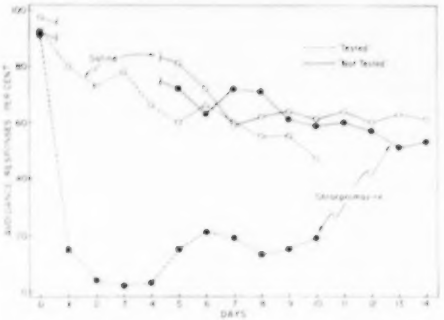
The animals were first given avoidance conditioning training. The subject was placed in the apparatus and given a one-minute adaptation period prior to the first trial. The buzzer was presented at the start of a trial and continued to sound until the animal had moved across the barrier into the other compartment. If the rat had not made a barrier-crossing response within five seconds after buzzer onset, the shock was automatically delivered to the grid and both buzzer and shock continued until the barrier was crossed. The CS or CS-US was terminated contiguously with the crossing response. The response was defined as moving from one compartment over the barrier and into the adjoining compartment with all four feet. Fifteen conditioning trials were presented daily for the 10-day conditioning period. The technique of progressively diminishing the intertrial interval during the conditioning phase was employed. This method has been shown to produce a rapid and stable avoidance response which is markedly resistant to extinction.[5] With this procedure, the intertrial interval was diminished from an average 60-second interval, at the beginning of conditioning, to an average 20-second interval, at the conclusion of conditioning trials. All extinction trials were run with an average intertrial interval of 20 seconds.

Ten of the animals failed to achieve the criterion of avoidance conditioning (70% or more avoidance responses for two consecutive days) and were dropped from further participation in the experiment. The remaining 52 rats were randomly assigned to four groups. Group I (N=11) was a saline control group, which received subcutaneous injections of 1.25 ml. per kilogram of body weight of isotonic saline each day for four consecutive days. Two hours after the injection they received 15 extinction trials in the conditioning box; i. e., the buzzer was presented but shock was not applied to the grid. If the barrier-crossing response had not been made within five seconds, the buzzer was terminated by the experimenter. Group II (N=15) received subcutaneous injections of a solution containing 1.25 mg. per kilogram of chlorpromazine daily for four consecutive days. Two hours after drug administration they were given 15 extinction trials in the apparatus. Group III (N=15) received injections of 1.25 mg. per kilogram of chlorpromazine for four consecutive days, but the animals in this group were not tested in the apparatus on days when they received the drug. Instead, they were returned immediately after the injection to the living cage. Group IV (N=11) received injections of 1.25 ml. per kilogram of isotonic saline for four consecutive days but were not tested on these treatment days. As in Group III, the animals of Group IV were returned to the living cages after injection.

Following the initial four days, during which the treatments were administered, all injections were discontinued. Groups I and II continued to be tested daily on an extinction procedure until they had a total of 150 extinction trials. Groups III and IV were also tested on extinction, beginning with the fifth day, i. e., 24 hours following the last injection. Groups III and IV were also given a total of 150 extinction trials at a rate of 15 trials per day. The design is summarized in the accompanying Table.

Summary of Testing and Treatment Schedules for the Four Groups

Group	N	Conditioning	Extinction	
		10 days	Treatment Phase 4 days	Post-treatment Phase
I	11	150 trials	Saline 15 trials/day	15 trials/day 6 days
II	15	150 trials	Chlorpromazine 15 trials/day	15 trials/day 6 days
III	15	150 trials	Chlorpromazine Not tested	15 trials/day 10 days
IV	11	150 trials	Saline Not tested	15 trials/day 10 days



Effect of chlorpromazine on the extinction of a conditioned avoidance response.

The extinction period began at Day 1. The tested group consisted of animals exposed to the experimental situation for the first four days, while the nontested group consisted of animals which were kept in their usual cages. All animals were treated with saline or chlorpromazine during Days 1-4.

Results

The extinction data are shown in the Figure. Inspection of the number of responses during extinction, particularly within the treated-tested group (Group II), indicated that the distribution could not be assumed to be normal. For this reason, the data were analyzed by means of the Fisher Exact test.[3] It was found that the treated-tested group (Group II) made significantly fewer conditioned avoidance responses ($P=0.01$) during extinction than did the saline-tested animals (Group I). Likewise, Group II made significantly fewer avoidance responses during extinction than did either Groups III ($P=0.01$) or Group IV ($P=0.02$). Alexander's test for trend[4] indicated no significant trend in Group II for the 10-day extinction period. Inspection of the data showed that the apparent upturn in conditioned responses during the final six days of extinction was a function of responding on the part of 4 of the 15 animals in Group II.

The Fisher test indicated no significant differences in number of avoidance responses during extinction in Groups I, III, and IV. There were no significant differences in trend of the extinction curves of these groups, according to the Alexander test.

Comment

The present experiment was designed to determine whether the failure of animals to make conditioned avoidance responses following several daily treatments with chlorpromazine was attributable to an accumulation of the agent with toxic effects or to relearning while the agent was affecting the subjects.

The results indicate that treatment with chlorpromazine in the amounts employed significantly suppressed the conditioned avoidance behavior of animals tested while under the influence of the drug. Moreover, daily injections of the drug for four consecutive days produced an effect on avoidance responding in those animals exposed to the test situation during treatment which continued for the remainder of the 10-day extinction period.

Had the factor of accumulation of the agent or toxicity accompanying repeated injections been important, the treated-not-tested rats should also have manifested a very low level of avoidance behavior during the course of extinction trials. Since the Group III animals, which were treated with chlorpromazine but not exposed to the test situation during administration of the agent, did not differ from saline controls upon resumption of testing, the toxicity factor could not be important in the persistence of effect found in Group II.

Neither the administration of chlorpromazine for four consecutive days with no testing during this interval (Group III) nor simply cessation of testing in the absence of the drug (Group IV) was found to have a significant effect on avoidance behavior when testing was resumed.

It appears that the crucial factor in disruption of the CR for the animals in Group II was the exposure to the conditioning situation at a time when the chlorpromazine was affecting the animal. Since the conditioned avoidance remained at a low level after cessation of drug administration, and since the data from Group III indicated that this is not a toxic effect, the treated-

tested animals apparently learned during the four treatment days that the buzzer was no longer followed by a painful shock, and this learning, persisting to the untreated conditions during the remaining six days of extinction testing, resulted in a failure to respond to the CS.

As Brady has pointed out,[5,6] in the assessment and interpretation of behavioral effects of pharmacological products, it is necessary to consider the action of the agents on the several systems which play a role in the behavioral response. Chlorpromazine has a "tranquilizing" effect when used clinically. This implies that the drug has some effect on the central nervous system which alters responsivity, particularly with reference to stimuli which induce fear and anxiety. The present study was designed to measure the effect of chlorpromazine on response to a fear-producing situation, i. e., avoidance conditioning. It was therefore essential to demonstrate that the cessation or diminution of avoidance responding subsequently to chlorpromazine administration was not attributable to motor deficit. A previous study[7] provides evidence on this crucial question.

In that experiment, a group of rats was trained to run an 8-foot runway to escape shock. Trained animals injected with isotonic saline were found to traverse the alley in 2.12 seconds. When these rats were injected with 1.2 mg. per kilogram of body weight of chlorpromazine two hours prior to the test, their mean running time was 2.85. The difference between the speed of running under saline and that under chlorpromazine conditions was significant beyond the 0.01 level. Thus, it may be concluded that chlorpromazine does have a demonstrable effect on this motor task.

In order to determine whether this retardation in motor behavior was sufficient to account for the effect of chlorpromazine of extinguishing an avoidance response, another agent having motor effects was tested. Phenobarbital sodium was selected for investigation, since it is a central nervous system depressant and produces, in sufficient dosage, measurable motor deficits; yet this drug is not ordinarily classified as a tranquilizing agent. Consequently, the animals were treated with graded doses of phenobarbital sodium to determine the amount of this material administered two hours before testing which would produce a running-time deficit equivalent to that of 1.2 mg. per kilogram of chlorpromazine. It was found that 40 mg. of phenobarbital sodium per kilogram of body weight increased the running time to 3.09 seconds, a level not significantly different from 2.85 seconds following chlorpromazine administration.

Additional groups of rats were avoidance-conditioned, using the same apparatus and procedure outlined in the present study. After conditioning, the rats were injected with 40 mg. per kilogram of phenobarbital ($N=10$) and 1.2 mg. per kilogram of chlorpromazine ($N=9$). At periods of two and four hours after injection the animals were tested in the conditioning apparatus, using an extinction procedure. The level of avoidance behaviors on the part of chlorpromazine-treated animals was markedly depressed, while that of the phenobarbital group was unaffected. The differences between groups were highly significant ($P=0.001$). Accordingly, it was concluded that, although chlorpromazine administration does produce motor effects, these deficits do not account for the dramatic effect of the agent on avoidance behaviors. These experiments are more fully detailed elsewhere.[7]

Clinically the effect of chlorpromazine and other "tranquilizers" has been described as the alleviation of "fear," "anxiety," and "tension" in emotionally disturbed patients. Experimentally these agents suppress responses to conditioned stimuli which are "fear-evoking." Further, although chlorpromazine has a measurable effect on motor responsivity, the effect is not large enough to account for the striking deficits in response to avoidance stimuli. The present study suggests that learning proceeds dur-

ing chlorpromazine treatment in that the rats did not respond to a conditioned avoidance stimulus after cessation of the treatment with chlorpromazine. These findings are consistent with the premise that chlorpromazine and other tranquilizing agents have an effect upon emotional responsivity.

The demonstration that relearning does occur during chlorpromazine administration suggests that long-term therapeutic results from the use of these agents may occur because the anxiety-reducing effects of the ataractics permit more appropriate, new responses to stimuli which previously induced anxiety. The data from the treated-nontested group (Group II) suggest that chlorpromazine per se has no persistent therapeutic effect unless the opportunity for relearning is afforded during the administration of the agent. Accordingly, therapeutic responses in clinical disorders may be anticipated if the ataractics are utilized as an adjunct to psychotherapeutic procedures.*

Summary

Fifty-two rats which had been conditioned to hurdle a barrier to avoid shock were randomly assigned to four extinction groups. Group I received daily injections of saline and was tested in the conditioning situation for four days. Group II was tested for four days after a daily injection of chlorpromazine. Group III was treated with chlorpromazine for four days but was not tested during this period. Group IV was treated with saline for four days but was not tested during the treatment phase. Following the treatment period each group was given daily tests until a total of 150 extinction trials had been administered to each animal.

It was found that the treated-tested animals (Group II) extinguished the avoidance response during the treatment period and that extinction persisted throughout the post-treatment period. The treated-not-tested animals (Group III) were found not to differ from either saline control group during the post-treatment period.

The result indicated that the persistence of extinction of the avoidance response in treated-tested animals was not attributable to an accumulation or a toxic effect of the chlorpromazine. It was suggested that the findings were attributable to relearning of the avoidance situation by animals during administration of chlorpromazine.

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* Clinical data reported by N. W. Winkelman Jr. (An Appraisal of Chlorpromazine: General Principles for Administration of Chlorpromazine, Based on Experience with 1,000 Patients. Amer. J. Psychiat. 113:961-971, 1957) provide evidence that more persistent therapeutic effects are obtained when chlorpromazine is used as an adjunct to psychotherapy than when the drug is used alone.

Schizophrenia and Task Orientation

The Structured Ward Setting

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Theoretical formulations concerning the cause, nature, and mode of treatment of schizophrenia are many. In actuality, however, there are currently three major formulations. One is a physiological concept based essentially on the principle of autointoxication, in which, although no specific factor has been found, there is a feeling that one will soon be found. Each year a new outcropping of possibilities appears, most of which readily yield their promise or appear to be simply correlates of an ongoing situation.[1-4]

Another formulation regarding schizophrenia, particularly etiology, seems to be the ubiquitous one of a congenital illness, primarily based on studies of twinning.[5,6] One area of comparative evidence for this is the model of Friedreich's cerebellar ataxia, which is an irreversible process, as might be expected of an illness of this type. In effect, the congenital or hereditary hypothesis is a rather indirect way of imputing a physiological base to the process and perhaps puts it in the class of a brain damage which is congenitally foreordained. To assess the nature of the effect of twinning would require adequate studies of twins reared apart.

There is something suggestive of other congenital and hereditary processes in the apparent onset at a certain stage in life and a course of remissions and exacerbations in the nature of schizophrenia. This is reminiscent of such processes as sickle-cell anemia and similar illnesses. But such evidences as we have at present could equally command a purely environmental hypothesis for the genesis of schizophrenia.

The third class of hypotheses is the environmental. In this set of theories the influences of early training, familial participation, and notions of deprivation, rejection, and overprotection are often brought into play. It may be said that, in a sense, none of these hypotheses is really contradictory but that each may complement the other in that a congenital base may provide the background on which a particular environmental set may induce a physiological disorder.

Many experiments and studies have been promoted on the grounds of one or another of these hypotheses, and at least the first two go back almost to the dawn of thinking about such things. Geneticists, including presently such figures as Linus Pauling, are pursuing factors related to origins. Physiologists are tending to mine in the direction of theories concerning physiological disturbances and agents to intercede on a physiological basis, such as tranquilizers.

Probably the answer to this question will remain a mystery for some time to come. Nonetheless, on the basis of clinical observation and experimental data with a particular ward setting, I should like to present some evidence in favor of an environmental formulation.

The present formulation, which derives from the clinical data, actually tends toward a new view of the interactive process and the development of patterns of interaction. Many of its implications remain to be explored. Essentially, however, the view is

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taken that the patients have developed in a situation where maladaptive patterns have been learned. When these maladaptive patterns no longer work for the patient in the face of unaccustomed demands, then the symptoms of schizophrenia present themselves. The therapeutic approach, therefore, tends toward the unlearning of the maladaptive pattern, the learning of more purposive and constructive patterns; in fact, a kind of habilitation process.

On the basis of the evidence, and in terms of the model to be presented, I believe that this particular brand of mental illness may yet yield to rational procedures, and not seem so hopeless as it often does. I recognize quite well that a certain proportion of schizophrenic patients may ultimately prove to have physiological or congenital components as a part of the origin of their illness, but I believe that this group, if it does appear, will represent only a small portion of the people presently described as schizophrenic. A greater number will, I feel, eventually prove to fit into the category to be described below.

Procedure

The patient population was a small, randomly selected group in terms of the variables that were explored. In a very real sense these were privileged patients who had the opportunity to be on a ward at the National Institute of Mental Health. They were in number 11, 4 women and 7 men. Diagnostically, in the usual category, they represented three with paranoid, one with simple, three with hebephrenic, two with catatonic, and two with childhood schizophrenia as adults. These patients were available for long-term intensive investigation on a 24-hour basis.[7,8]

All of the patients had been hospitalized for periods ranging from 4 to 17 years, a total of 97 hospital years and a mean of about 9 years. The ages ranged from 22 to 51 years; all but one patient were under 40 years of age. They had run various courses but, once having gotten into the hospital circuit, tended to remain with no spontaneous remissions or periods of adequate function outside the hospital situation. The patients had had histories of periods of quiescence and activity. On entry into this setting, three were relatively highly organized; eight were quite regressive and, occasionally to frequently, assaultive. The population ranged in previous accomplishments from finishing college (two) to not finishing high school (four). Two had succeeded in holding a job for more than a few months prior to hospitalization, and the rest had required almost continual outside support.

It was possible in this quite unique situation to enlist the support of five sets of parents, one mother, and one husband regularly. One other father, one other mother, and one other husband could be enlisted on a contingent, but not continuous, basis. There was one twin in the group, the identical sibling of whom, as well as two other siblings, was also hospitalized. The patient group had 12 other known siblings, all of whom were apparently relatively successful.

One mother of one patient and the father of another were known to have had psychotic periods in their lives preceding the illness of their children.

The opportunity provided in this setting was indeed unusual. The staff was headed by *one* ward administrator-therapist, thus alleviating many of the inbuilt problems of dividing these functions, as in other similar settings. He was the only physician in continuous contact with all the patients. Five of these patients (one catatonic, one hebephrenic, one paranoid, and both autistic adults) were seen in individual sessions twice a week. The entire group was seen in patient-staff meetings with the administrator once per week, and a separate parent-staff-administrator meeting was held once a week, on Saturdays. The ratio of patient-to-staff population ranged from 8-9 patients to 4-3 staff during the 8:00 a. m. to 4:30 p. m. shift and from 8-9 to 3-2 during the evening and night shifts. No form of seclusion or restraint was employed. No sedation or tranquilizers were employed for management or disturbances. The staff was thoroughly and continuously indoctrinated with the goals, techniques, and theories underlying the procedures employed, as were the parents.

The function and mission of the group was to test out certain hypotheses regarding the nature of patient behavior and techniques which might be employed both to manage the patients and to promote changes in terms of greater socialization and preparation for return to the community at large. Acting out was discouraged, and assaultive behavior was physically suppressed, although as soon as the patient became quiescent he was immediately reintroduced into the group. There was no period of compensatory seclusion or punishment in any form. Self-seclusion on the part of the patient was prohibited. Participation in activities was mandatory; not merely presence but actual involvement was required, and this rule was enforced. The patients who had done nothing for themselves in the way of personal care for years were required, and, if need be, forced, to assume the care of their

personal hygiene; chores, such as cleaning rooms and policing the areas of activity, were required; the group participated as a whole in all activities, many of which were in the outside community, and no exceptions were made, regardless of how disturbed a particular patient seemed. Gradually, a work program, including Goodwill activities, such as furniture repair and refinishing, clothes mending, button sorting, and a letter shop, was set up and enforced such that the patients were required to produce and no excuse was permitted for nonperformance, the patient being harassed until he did perform. A newspaper was begun of patient productions, no matter how bizarre and disturbed. Individual activities, such as jobs off the unit, like typing and others, were promoted and carried out. The parents were indoctrinated with the purposes and methods and after the Saturday sessions took over the patients for the next two days, at first in terms of a few hours, later in terms of weekends and trips out for a week or two at a time.

Results

It is not so much of the results of these procedures that I wish to speak at the present time as of certain features of behavior and their implications which became prominent in the course of the year of the experiment. As far as results themselves are concerned, it was felt that three of the patients, with proper support and guidance, would have been able to function adequately on the outside even before inclusion in this setting, despite considerable hospital experience. One other patient after two months on the ward wrote his first letter in 17 years of hospitalization and, despite a history of protracted and stormy illness, after six months was ready for discharge home. Three others on the ward, with gradual support and progressive reduction of protection, would have been able to return to functioning relatively effectively outside the hospital setting. These included one "autistic" adult, one hebephrenic, and one paranoid, all quite regressed at the beginning of the experiment. One other patient was prematurely returned, for unrelated reasons, to another hospital when signs of greater socialization were in process, but we had not had time to see conclusive change. Two others were improved and improving, but a longer time in the setting would be required to bring them to the level of the rest. One patient who was gradually improving had been only recently introduced to the ward setting, and it seemed too early to make a conclusive statement about his progress.

At the expiration of the year assaultiveness had progressively decreased to almost none from at least one episode per day initially. The appearance of the patients had improved markedly, particularly of several, so that, as many outsiders who saw the group noted, "They no longer look like patients." Performance in the work group was at a high level of proficiency (a 5000 envelope job in the letter shop had been finished in about four days toward the end of the period of observation reported). The patients were all taking care of their own hygiene and appearance at the end of the year, mostly spontaneously, although several with no great relish.

Patterns of Interaction

In the course of the year a number of things caused me to revise my thinking about this group of patients, and perhaps particularly their interaction with parents. The implications of these revisions were extensive in terms of my own notions of pathogenesis, prevention, and therapy. As the work progressed, one patient after another became the focus of attention. Many problems, not so much in the thesaurus of psychodynamics as in that of common experience, came to the fore. Recalcitrance, manipulation, reluctance, deviation, pseudofatigue, indifference, playing possum, indolence, helplessness, aggressiveness, avoidance, self-seclusion, and other kinds of interaction were prominent. After a weekend with the parents the patients were often said to be conspicuously "worse than ever." Certain behavior on the part of the parents was often quite obviously assumptive of too much of the "decision-making responsibility" [7] for these people, even, for example, such items as holding an ash tray or a Kleenex for themselves. A great deal

of caressing on the part of the close relatives was evident, particularly regarding two of the more "helpless" patients, one of whom was also quite assaultive periodically. It was said on one occasion that one father "did not have the patience we had" and had shaved his son (age 22) on a weekend out. In the ward setting the patient was, however, quite capable of shaving himself. This information evoked the fact that the father of another, an "autistic" son, had shaved his son continuously until hospitalization, four years before. Another patient had been provided a new house each time she asked, from her husband; another, a horse and all possible advantages, including the development of a school on the part of her mother, primarily so that she should be properly educated. Another patient's mother had continuously brought food to her daughter's house, even after she was married, and repeatedly disapproved of her husband. If these subjects were deprived or rejected in the ordinary sense, it was certainly not apparent. If anything, from discussions with parents, it appeared that the sibling who had not gotten sick and was successful had often been quite literally, by contrast, given second best at home. For example, the sister of the patient who was given the horse received a pony, in a home setting which could have provided equal treatment for the two. Or, in another situation, the sister of one of the autistic men had had to shift for herself, while the patient's family moved in order to accommodate itself to his "needs."

Corrective Patterns in Setting

In terms of the structured ward setting, on the other hand, certain phenomena of interactive behavior were conspicuous. The patient's initial reluctance to participate verbally and nonverbally was prominent. Nonetheless, when a "no" of the patient was ignored and participation was pressed anyway, the nonparticipation gave way regularly to an operation which might be called a "give-in phenomenon." In effect, the patient seemed suddenly to say or to act in such a manner as to communicate, "Well, of course, why didn't you say so in the first place?" If, despite a great number of patently diversionary tactics, the person working with the patient remained insistent, the patient would often perform the task, occasionally even admirably, an operation which we tended to call a "carry-through phenomenon." If the patient had responded assaultively, but still task completion was insisted upon by the person who was working with him, the patient might afterward tend conspicuously to favor the person he had assaulted or even thank him in words, apologize, or bring him something, such as a cup of coffee, behavior which we called a "thank-you phenomenon."

These responses were noted particularly as the patients were forced more on their own initiative in task completion, often despite objections. They would make such comments as "I don't want to make the bed"; "Won't you wash my back?"; "If I shave correctly, I'll get well and get out of here, and I don't want to do that," or "He says I have to shave right, not everybody has to shave right." One patient, who was called a paranoid because he said he heard voices,[9] perhaps franker than the others, said: "I don't want to leave the hospital; I like asylums; I guess I'll spend the rest of my life in one."

One autistic patient was quite remarkable for the many minor variations he could introduce into a task, a performance which could not have been anything but intentional and deliberate. If asked to write "A," he wrote "B" consistently in one session, during which he was pressured to review the alphabet. As on another occasion, when he was asked to write "Esso," he wrote "Amoco" regularly in copying a page of reading.[9] He had developed on another occasion 30 separate errors in the task of pasting an address tag on an envelope, thus requiring the correction of someone continuously beside him. The patients regularly would either resist beginning a task or find

some rather subtle way to protract it, turn it aside, ruin it, or discontinue it. Many times the patient would accompany this behavior with a wry smile or guffaw. One patient, in the face of task expectation, displayed the most beautifully sardonic smile as he set up one booby trap after another for the staff.

Since the task was our measure of action and function, this was the chosen arena of contest for the patient. It also became apparent that, if task completion was not insisted upon, the patients tended to become quite angry, or even assaultive. To be "permissive" with them seemed to promote disturbances and acting out, almost in a self-regenerative fashion. This was particularly evident if the thing "permitted" was patently absurd by ordinary standards. It was almost as though the patient were saying, "If you have such little respect for me and for yourself, I'll show you how foolish I can make us both look"; or the patient would openly say, "You don't know what you want or what you are doing," or would begin to ask for the "president" or some authority to set things straight.

Concentration on the "task" in this fashion gave us the opportunity to look at task orientation in the schizophrenic. It was clear in this group that the patients were loath to begin a task requiring effort, loath to do it right or continue, and often loath to stop when the time to do so was declared, even if they were not actually achieving anything by the way they were performing it.

Comment

There are four major periods in the life of the individual when the possibility of a schizophrenic reaction is high. These are (1) at about the age of 3 to 5, in the preschool era, when the child is beginning to make movements outside the home situation; (2) the postpuberal period and the early 20's, when he is finishing high school, or going to college or work; (3) the period of the climacteric or of job decline; (4) the period of the death of another, the departure from home of a child, or acute stress of one sort or another. Each of these periods represents a time when restructuring of the patient's world is demanded.

All of the patients in this study fall into one or another of these categories: Two apparently became sick at a preschool period but were compensatorily handled for some time; two at the age of 16, prior to completing high school; another before leaving college; another after leaving college; another at the gradual moving of her daughter out of the household and, finally, marriage; another on the departure of her husband overseas; another following divorce, etc. Critical changes in status were occurring, such as need for self-support, responsibility for one child and another on the way, responsibility of raising two sons acquired later in life when a daughter 13 years their senior had always taken care of them, being on one's own in the neighborhood and school, having to find employment out of government, etc.; such shifts, whether gradual or sudden, in a very real sense entailed an increase or alteration in the number, diversity, expectation, and responsibility of tasks to be performed at a given stage in life and in a given setting.

The task concept, then, may be considered a focal unit in observing the schizophrenic. As a unit, the task once assumed must be carried to completion prior to the assumption of another job for normal load bearing. Such a task may be defined briefly as comprising an event, such as a conversation, thing, action, and the participation of two persons, either in immediate proximity or at a delay in time or space.*

Often sudden transitions to fuller load bearing occur at periods when the stability of other structural supports is diminishing, such as the home, parents, friends, school,

* This may be related to the POX unit of Heider [9] and the conversational unit of Newcomb.[10]

etc. This situation is reminiscent of what Durkheim [12] called *Anomie*.†

Perhaps it would be useful to put aside briefly two concepts which I think fail to characterize the situation. One is overindulgence, which implies that excessive demands should be gratified. This I do not believe is primarily the problem in schizophrenia, although it is one of the more popular recommendations for treatment. However, it is limited by essentially perpetuating task incompletion and institutionalizing task assumption from outside. The other concept, which should be put aside, I believe, is that of rejection. Particularly apparent in this group of patients, this was not in any sense the situation. In fact, it would appear that it might have been better had they been rejected a bit more, so that they might have developed the capacity for responsible decision taking and task assumption if these followed from their being pushed out of the nest.

Rather than either of these ideas, and maintaining the frame of reference of the work load, it would seem to me that these people are chronically underloaded or lack the capacity to shift to greater load bearing under stress. Thus, if a hypothetical load for a task is about 40% normally and the maximal load 60%, these people are functioning at 20% or less of load capacity for the given task in their prepsychotic experience; 5% to 20% is assumed by one or both parents or is not assumed in response to conflicts between the parents.‡ This may go under the guise of infinite patience for an inadequate and uncorrected performance, or impatience such that the task gets taken from the patient, who then fails to gain personal experience in completing it. One might compare here Ruth Benedict's description of task setting and task expectation among the Papago Indians, as quoted in Erikson's "Childhood and Society." [14] No task will be set which is too difficult for the child, but once it is presented it will be expected that the child will carry it to completion.

This analogy may be carried further in terms of load-bearing capacity. If a normal person in a job is given more than he can do, in other words, is flooded or overloaded, a characteristic response ensues, from the experiences of studies in work performance.[15,16] Instead of omitting the items he cannot handle and doing only that which he was successfully handling before overloading, the individual "blows up," that is, becomes incapable of doing anything at all. The analogy is startlingly reminiscent of what happens to the chronically underloaded patient, who may be devastated by sudden confrontation with a load appropriate for the situation others are bearing in the community under similar circumstances.

Such crises may be resolved by the assumption of an even greater portion of the load by the parents, thus sparing the child the necessity of learning to bear his own load. This happened conspicuously in the case of the autistic children of this group. Neither was required to make any effort; and, regardless of what each did, the parents continued to pretend, on good advice, that a child who was not performing was just as well off, without any necessity to do so, and that he should be provided with the symbols of success anyway.

Another alternative for normal load assumption is that someone else may assume the load for the individual outside the home, such as hospital, therapist, or friend; or a load sustainer or substitute, such as drink, drugs, or promiscuity, may be employed. A more constructive alternative might arise from an outsider who insists that the individual can sustain his own load, and thereby helps reframe the structure in which

† Durkheim's concept is developed in the context of a discussion of suicide. A parallel may be noted in the suggestive use of the word "dead," which often appears in the schizophrenic's description of himself or his state. It may be that the schizophrenic maneuver is an alternative to the resolution of suicide.

‡ Whitehorn [13] suggests that from the standpoint of the patient there is a "lack of commitment" to the task, or perhaps to the concept of task bearing.

the patient may then move toward survival and growth.

This kind of positing of a path, but insisting or encouraging the patient to follow and open it, may be called "channel sitting." Aberrant paths must often in such circumstances be blocked if possible; that is, "limit setting," in order to delimit the confines of task consummation.§ Each of these actions tends to reinforce the self-respect and capacity of the patient, since he knows that something is expected of him within the structured world in which he has a functional place. Respect is communicated by the insistence on function, rather than the disrespect of directly or indirectly communicating to him that he is capable only of performing in an aberrant fashion or of doing nothing at all. Perhaps this may be too simple a formulation of a process which appears so complicated and compounded, but if there is not a learning deficit,[17,18] what kind of deficit is there?

Conclusion

In a purely operational, almost operant, setting[19,20] I have probed some of the parameters of task performance for a group of predominantly severely retarded patients. Instead of discovering blocks to task performance on the basis of inability to perform or to learn, I found that discrepancies of performance had a quality of deliberate resistance, both calculated and bemused. It may be not for nothing that the hebephrenic laughs. However, when performance of an appropriate and orderly type was insisted upon, the resistance gave way and a new kind of relationship seemed to be forthcoming. This was in a sense a relationship based not so much on "insight" in the usual sense but perhaps more in terms of "outsight" or "other sight." An awareness of self in relation to task and both of these in relation to other persons seemed to develop. The patients began to function more efficiently and apparently to grow in self-esteem and the esteem of those about them.‖

Permissive lack of identity and irresponsibility have been discouraged and responsible load assumption encouraged. Task unit completion has been devised as a standard of reference for exploring this. In this light, one might do well to examine the relationship between such a conceptualization and the usual postulates of illness. Such an actional frame of reference also permits a review of the patient's verbalization, perhaps less as reliable reportage than in terms of a form of task behavior itself, and subject to similar rules.

The introduction of a structured setting into the aberrant world of the patient tends to provide an orientation within which the patient may derive some sense of order and relatedness.[21] The use of this point of departure, comprising limit- and channel-setting procedures, may lead us to a better understanding of the schizophrenic and hopefully to methods of rehabilitation of the chronic, particularly the regressed, patient.

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§ The tranquilizers may function in the capacity of chemical limit setters; however, this is only part of the job to be done with the schizophrenic patient.

‖ In fact, some of the staff seemed disturbed that the patients were no longer quite so "crazy" and seemed to lose interest in them as they changed. One might speculate whether or not the staff, as the patients became less dependent, did not feel underloaded themselves in the face of less to do for and with the patients. It is not uncommon that the staff seems reluctant to return to a patient his freedom and responsibility, particularly in a hospital setting. Perhaps this is a clue to one of the factors inherent in the hospital itself and in people around the patient which may tend toward the perpetuation of the illness actually on a societal basis.

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Effect of Synthetic Diet Low in Aromatic Amino Acids on Schizophrenic Patients

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This paper describes the effects on young hospitalized schizophrenic patients of a diet essentially free of aromatic amino acids. The metabolic effects of such a diet, as reflected in the content of "aromatic" compounds in blood and in their excretion in the urine, form the subject of a separate communication. The present paper will be concerned only with the clinical changes observed in the patients.

Method

Patients Studied.—Twelve female and eleven male patients were selected at random by the clinical chiefs of service with the following criteria in mind: 1. They were to be less than 35 years of age. Four were in their late teens; two were 31 and 38, respectively, and the rest were in their 20's. 2. Patients were sought who had recovered from previous acute psychotic episodes in hospital, so that more information might be available regarding their behavior during these periods, and that as adequate a history as possible might also be available. For 1 patient this admission was the fourth; for 4, the third; for 11, the second, and for 7, the first. 3. Together with the history of previous admissions to hospital, it was expected that these patients would have shown a response to other therapies which was sufficient to permit their return to the community. Thus, of the 16 patients who had had previous admissions, 2 had improved with chlorpromazine (Thorazine); 1, with ECT; 1, with coma insulin; 9, with a combination of ECT and insulin, and 2, with a combination of chlorpromazine, ECT, and insulin; and 1 had recovered without any of these three. In no case had intensive psychotherapy been used. Of the seven patients for whom this admission was the first, two had shown temporary improvement with a combination of ECT and insulin but had relapsed; one had shown no response to insulin; one, no response to ECT, and one, an inadequate response to chlorpromazine; two patients had not yet received any definitive therapy.

Thus, of the 23 patients studied, 19 had shown their ability to recover from an acute psychotic episode for varying periods of time. The patients were told specifically that the diet was a therapeutic agent which, it was hoped, would be of help to them. All patients were together in a separate closed ward which contained male and female dormitories and a common area. They engaged in outdoor activities, as well as indoor occupational therapy, under close supervision.

The Diet.—The deficient diet, first used by Woolf et al. in the treatment of phenylketonuria,[1] contained negligible amounts of aromatic amino acids. This was accomplished by the use of a casein hydrolysate as the sole protein source. This material had been essentially freed of tyrosine, tryptophan, and phenylalanine by acid digestion and elution on a charcoal column.* The casein hydrolysate was prepared as a soup which contained, in addition, wheat starch, sugar, margarine, peanut oil, tomato juice, and chopped onion (0.1 gm. protein, 6.2 gm. fat, 17.2 gm. carbohydrate, and 124 Cal. per serving). The soup had a dull, flat taste. Other foods included fruits (e. g., apple, grapefruit, orange, pineapple, strawberries, plums, pears), vegetables (e. g., tomato, rhubarb, carrots, lettuce), bread (made with wheat starch, margarine, pectin, and sugar), wheat cakes, cookies, puddings, iced cakes, tea, coffee, and lemonade. The caloric intake was between 2400 and 2700 Cal. per day. The unavoidable protein ingested in the test diet did not exceed 2.5 gm. daily. Clusivol (multivitamin and mineral) capsules were given once daily to ensure adequate vitamin intake.

All patients received the deficient diet for three weeks. At the end of this time, for a second three-week period, one-half the patients (six females and five males) remained on the deficient diet, while the rest had phenylalanine (5 gm. per 100 gm. of protein) and tryptophan (1.8 gm. per 100 gm. of protein) added to their soup to provide an adequate daily intake of aromatic amino acids. The assignment of patients for the control diet of

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* Allen and Hanburys, Ltd., Bethnal Green, London 21.

the second period was made at random by the dietitian, in advance of the first dietary period. It was impossible to distinguish the deficient diet from the control diet in terms of appearance or palatability, and neither the patients nor the staff were aware that there were two diets. The establishment of a closed metabolic ward with a specially assigned nursing staff ensured against the possibility that food other than that on the diet would be available to the patients. Failure to ingest portions of the soup was recorded. Two patients who consistently refused the soup which contained the aromatic amino acid supplement had to be considered on the deficient diet despite the fact that they were intended to be controls.

Evaluation and Controls.—In addition to the division of the patients into two groups with respect to the true and simulated diets described above, two members of the nursing staff, one male and one female, were placed on the deficient diet. Clinical evaluation of the patients' progress was made by psychiatric interview and, independently, by the observations of the ward staff. Each nursing shift described the behavior and physical condition of the patient on a printed form and also wrote a daily note describing any perceptible change in behavior. The patients were evaluated for one week prior to the institution of the diets, as well as during the dietary period, when patients were seen daily and interviewed at some length once weekly. The staff psychiatrists visited their patients every few days, maintaining contact with them but refraining from any intensive psychotherapy.

The dietitian alone knew which patients were on the deficient diet and which were controls, and she had no personal contact with the patients.

Results

Of the 22 patients on the deficient diet (1 left on the third day of the diet), 13 (8 males, 5 females) were clinically worse, and 9 showed no significant change.

In the second three-week period, of the 13 patients whose condition had deteriorated, 1 had to be removed from the project to be given ECT, 8 remained on the deficient diet, and 4 fell into the control group receiving an adequate intake of aromatic amino acids. Of the eight who continued on the diet, five remained worse, while three returned to their prediet level (still unimproved). Of the four who subsequently received an adequate amino acid intake, all showed improvement. One was better than her prediet level for a week and then slipped back again, while the other three gradually improved to their prediet level of adjustment only.

Of the nine patients (two males, seven females) who showed no significant change in the first three weeks on the deficient diet, five fell into the group remaining on the deficient diet, while four received the adequate control diet. Of the four who received an adequate intake, one improved to a slightly better than prediet level, while three showed no significant change. In the five who remained on the diet, no significant change occurred.

The criteria for evaluation of improvement or deterioration were in each case related to the symptomatology which brought the patient into hospital and which would, by its persistence or augmentation, tend to keep the patient in hospital.

Of the 13 whose condition deteriorated, the psychotic behavior of 7 was egocentrifugal, while that of 6 was egocentripetal. These terms refer to the direction of ego energies with reference to the patient and the environment and are developed more fully elsewhere.[2] Thus egocentrifugal behavior is that directed outward, and would include overattention to people or things, overtly aggressive behavior, shouting, destructiveness, etc., whereas egocentripetal behavior is that directed inward, and would include increasing withdrawal, depression, negativism, catatonic behavior, self-mutilation, etc.

One patient whose delusional systems prior to admission included the fear that her food was being poisoned showed no significant change either in her ideation or in her behavior.

The two nurses who took the diet managed to tolerate it for only two weeks. They found they were irritable, and somewhat tense throughout, although it was the sheer boredom and flatness of the food which was most obviously responsible for the shortness of the trial. In view of this, it is of interest that only one patient elected to drop out.

All patients lost between 1% and 16% of their weight, the mean loss being 8.4%. There was no correlation between weight loss and clinical condition.

The spirit on the ward among the nursing staff appeared to be rather good throughout, although it became apparent in the weekly ward meetings that there was a good deal of uneasiness with regard to the restriction of food, to the experimental aspects of the treatment, and, as the condition of some patients deteriorated, to the withholding of the somatic therapies, which had previously been quite freely used in the nurses' experience. The attendance of between three and six nurses during the two daily shifts provided a considerably higher nurse-patient ratio than is commonly available, even in the setting of insulin coma therapy. The nurses gave a good deal more individual attention to the patients than is customary in the acute treatment setting.

The group dynamics among the patients was not unusual. There was a good deal of cohesiveness, and the mutual-aid activity, as well as the conflicts manifested, did not differ perceptibly from that seen on an insulin coma ward.

Comment

It is clear from the results presented that the diet given under the conditions described is not to be considered a therapeutic agent. In fact, there is evidence that it is psychotoxic. While improvements attributable to placebo effects or to spontaneous recovery would be expected to take place in about one-third of the patients, in the present experiment none showed any significant improvement.

On the other hand, it is indeed unusual in psychiatric therapy of any kind to witness a marked deterioration in the patient's condition. In the present therapy, a clinical deterioration was observed in 59% of the patients. This is especially surprising in view of the fact that the ward environment and the nursing care were of a high order.

While it is possible to formulate explanations for the effect observed, there is no evidence available at present which points clearly to the mechanism involved. It is of interest to contrast the present therapeutic results with those achieved in insulin coma therapy. Among the reasons commonly given for the improvement obtained with insulin are the special attention given to the patients and the communal experience on the ward. In the diet therapy described, all of these factors were strongly operant, even to the encouragement and feeding of the patients by the nursing staff when appetites lagged. One might say, perhaps, that while the factors enumerated are probably of some importance in the improvement of the patient, they were certainly not of sufficient importance to prevent the clinical decline in a large proportion of the present group. One is inclined to think either that there is something very specific in the meaning to the patient of insulin therapy, which is beneficial, or, more likely, that there is, in fact, a therapeutic metabolic effect operating in insulin therapy.

That a metabolic effect is responsible for the changes observed in this study is suggested, but not proved, by the fact that four out of four of the patients whose condition deteriorated on the deficient diet and who subsequently received supplementary aromatic amino acids improved, whereas five out of eight of those whose conditions deteriorated on the deficient diet and who continued on this diet remained worse than their prediet level. The possibility that the deficient diet is psychotoxic for only certain patients clinically diagnosed as schizophrenic would have to be further investigated with a larger group of patients. That the effect may be due to the presence in the deficient diet of traces of degradation products of the aromatic amino acids must be considered. This possibility will be tested in a later experiment, in which the products of acidic digestion (as employed in the preparation of the deficient diet) of aromatic amino acids is added as a supplement to a normal diet.

That nonmetabolic factors are responsible for the changes observed must be considered, since the deficient diet, although calorically adequate, was extremely austere (no milk, meat, or fresh vegetables), and the restrictive nature of the diet represented a negation of oral needs. The experiment presented, in a dynamic sense, a state of oral deprivation, and it may be that the gratification of oral needs is a crucial factor in the maintenance of the equilibrium of some schizophrenic patients. Despite this, the great majority of the patients chose to stay on the ward. This may be interpreted as evidence of the patient's masochism, but it may equally well be viewed as a striking example of the motivation of the schizophrenic patient to recover. That the psychotoxic effects of the diet cannot simply be explained in terms of an increase in "acting-out" behavior by the patients is indicated by the fact that egocentrifugal behavior did not predominate over egocentripetal and that the type of reaction of each patient was consistent with the previous history.

Summary and Conclusions

Twenty-three young hospitalized schizophrenic patients, most of whom would be expected to recover from their acute psychotic episodes sufficiently to return to the community, were placed on a diet grossly deficient in aromatic amino acids for three weeks, followed by a second three-week period in which one-half of the patients received a control diet, adequate in aromatic amino acids but indistinguishable from the deficient one. A "double-blind" method for control was employed.

Of the 22 who were on the deficient diet, 13 showed definite clinical deterioration, and none showed any significant improvement. These unusual results are contrasted with those which might be expected with placebo, insulin coma or any other known psychiatric therapy, and are considered in terms of the possible factors responsible for the beneficial effect of insulin therapy. It is concluded that the diet, as described, is not only non-therapeutic, but apparently psychotoxic. Some of the factors which may be responsible for the psychotoxic effect observed are considered.

Drs. A. M. Gee, A. E. Davidson, and F. McNair made available the clinical facilities of the Crease Clinic of Psychological Medicine and the Provincial Mental Hospital, Essondale, B. C., Canada, and the members of the nursing and dietary staffs assisted. This study was conducted under the auspices of Dr. W. C. Gibson and the Department of Neurological Research, University of British Columbia Faculty of Medicine, Vancouver, B. C., Canada.

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